U. S. FOOD AND DRUG ADMINISTRATION
REQUIREMENTS FOR TOXICITY TESTING OF
CONTRACEPTIVE PRODUCTS

By

V. R. Berliner

ABSTRACT

The evolution of toxicity testing of drugs in general, before and after the enactment of the Kefauver-Harris Amendments of 1962 to the Food, Drug and Cosmetic Act of 1938, and of the specialized requirements for test methodology to support the safety of systemic contraceptives are described, with comments on the organizational mechanisms for their implementation, for the interpretation of test results and for eventual regulatory actions and policies. The controversial long-range (life-time) studies in beagles and rhesus monkeys for hormonal contraceptives to predict their carcinogenic potentials are discussed. Results already obtained from these ongoing investigations suggest a hypothesis that in those hormonal contraceptives which are capable of inducing "atypical" nodules and/or malignant tumours in mammary glands of beagles it might be their chemical configurations that exert this reaction, along with their progestogenic potency.

Since the contraceptive compounds exhibiting these adverse properties in beagles have not been used long enough clinically to determine their carcinogenic or tumorigenic potential in humans, it is not possible to correlate these effects in the beagle to that in the human for these compounds. On the other hand, for OC's which have been approved for marketing and have been in wide and long clinical usage in the United States, no hazard in terms of increased tumorigenic or carcinogenic potential has been identified to date for the human and the beagle.

While metabolism studies with those contraceptive formulations that were
incriminated by their adverse actions in beagles have disclosed metabolic patterns and endproducts to be different in the beagle and human, a causative relationship between their metabolic endproducts and a tumor-ogenic and carcinogenic effect, especially with prolonged administration of these contraceptive compounds, has not been investigated. With these considerations, and because the suitability of the rhesus monkey as an animal model for carcinogenicity testing is questioned, it would be contrary to the spirit and intent of the existing drug safety regulations in the United States to eliminate the canine species as a test animal in carcinogenicity investigations to support the safety of hormonal contraceptives. Tentative guidelines for toxicity tests on new and forthcoming principles for contraception such as the prostaglandins, and IUD's serving as carriers of pharmacologically active substances, have been drawn up in consultation with advisory committees and will be discussed.

The invitation to the Food and Drug Administration to describe its regulatory requirements for toxicity testing of contraceptives brought with it the request to include the following topics which were presented in the form of six questions:

1. What is the history of FDA toxicology requirements of contraceptives?
2. Which contraceptives have specified FDA toxicology requirements and which have not?
3. How were the present requirements drawn up?
4. How successful have these requirements been and by what criteria?
5. By what mechanisms does the FDA evaluate toxicity requirements for new methods of contraception (as distinct from new products using existing methods)?
6. What are the review mechanisms for existing toxicity requirements?

The points raised by these questions are by no means original. A similar situation to to-day’s conference, with events particularly applicable to the matters of this presentation, occurred at The Conference on Contraceptive Drugs held in July of last year in San Francisco under sponsorship of the Drug Research Board and the Committee on Problems of Drug Safety of the National Academy of Sciences and the National Research Council. There was international representation at that meeting also. The goal was similar to that of this program, namely to identify areas in the field of fertility control in which research is needed. In the Workgroup on Problems of Regulation, chaired by Dr. H. Simmons, then Director of the Bureau of Drugs, now Deputy Assistant Secretary of Health, HEW, considerable time and effort was spent on debates and criticism of regulatory steps and attitudes by FDA relative to the toxicity
test requirements for contraceptives, concentrating mostly on their long range studies and the use of beagles in these tests. The main complaints were that the responsible FDA staff, in setting up these tests, had neglected to obtain beforehand expert advice from outside the agency, in regard to the appropriateness of these tests and the suitability of the beagle as an animal model for carcinogenicity tests for hormonal contraceptives. It was also claimed that the action taken by FDA against certain investigational contraceptives because of their effects on the mammary glands of beagles had been a glaring example of faulty execution of regulatory functions by FDA. As a remedy the creation of an appeal body, even of international standing, had been proposed, to adjudicate differences of opinion on scientific, industry and regulatory issues, and the formation of independent committees to review requirements promulgated by FDA, for their competence and value. In reply to these proposals for correction, Dr. Simmons had stated that plans are under way at the agency to rework some of the existing guidelines for pre-clinical testing. He also stated that guidelines are flexible and are changed in accordance with new information and knowledge as it becomes available in any given area. But he also pointed out that the agency constantly has to face new problems that have to be met in spite of the lack of adequate knowledge as to what would be sound requirements, and that somebody has to make a decision in the best way he can, in the public interest. He took a strong stand against the statement that FDA requirements for safety and efficacy are too stringent and cause undue delays in making valuable drugs available.

So, no matter from what angle we approach to-day's topic the matter of the long range studies will have to be dealt with and is best gotten out of the way first. In context with the above mentioned statement of Dr. Simmons' for the occasional need for actions before all the know-how is available, it has to be realised that the need for this concept was in force not only when the long range tests were introduced by the agency, but already earlier, at the very start of the area of oral contraceptives. Their mode of actions were not completely understood then, almost 15 years ago, they are not completely established even to-day, yet actions had to be taken in this scientific vacuum in both the clinical area and the area of testing these new entities in the animal model (what you call the toxicity test etc.). To have taken the stand to wait until all the facts are known, would have kept birth control and population control at the level of the vaginal spermicidal gels for years to come. In addition, all these happenings took place at a time when regulatory functions of FDA were undergoing drastic changes because of the enactment in 1963 of the Kefauver-Harris Amendment to the Food, Drug and Cosmetic Act, on safety requirements for new drugs. For a better understanding of this situation the meaning of this law has to be explained at this time. The law directs that a new drug must not be administered to a human until it has been investigated
by the sponsor for its extent of safety for human use, that is its hazardous properties, by appropriate tests in laboratory animals. The results of these investigations in animals must be submitted by the sponsor to FDA for evaluation by the agency’s professional staff, the pharmacologists, for their scientific validity to support claims that safety has been investigated and established. The drugs have to be investigated also for their functional properties. This legislation has removed many uncertainties that had existed heretofore in regard to procedures aimed at ensuring the safety of drugs. Until its enactment in 1963 the drug manufacturer had been responsible to ensure the drug’s safety, but it was left to his discretion and interpretation of his test results in animals whether the drug was safe enough to be administered to human patients to study its clinical effectiveness, and he was not required to submit these results to FDA for review until such time as he desired to market the drug commercially. Occasionally decisions on safety were made prematurely and not on purely scientific grounds. It was the aim of the new law to prevent the unnecessary exposure of humans to unsafe and useless drugs and also to safeguard the American people against a thalidomide-type tragedy. In an effort to comply with these new requirements of the Food, Drug and Cosmetic Act the pharmaceutical industry approached the agency for guidance with respect to the extent of the safety tests for all investigational drugs that would be acceptable to the agency as evidence that efforts had been made to establish and to describe the pharmacologic and toxicologic properties of a new drug and, thus to assess its safety. Guidelines for toxicity tests for all drugs were then drawn up by Dr. A. Lehman, Director, Division of Pharmacology, in accord with their intended clinical usage, duration of treatment, route of administration and so on. In line with the newly introduced system of progressive clinical trials by escalated phases, the extent of the toxicity tests to support the clinical phases were also set forth. The animal species recommended for these toxicity tests were rodents, rabbits, and dogs. Monkeys were at that time still a rarity. The breed of dog was not specifically named, but toxicologists in the States had been using the beagle breed for some time because of its convenience of handling and availability, so it was assumed that beagles would be it. The Lehman Guidelines, as they became known after their presentation at a Joint Symposium on the Safety Evaluation of New Drugs in 1963, did not contain a special category for hormonal, or any kind of contraceptives. Those under investigation at that time were tested under the category of toxicity tests for orally administered drugs for unlimited treatment periods of clinical use. Actually, the first contraceptives to obtain NDA approval had undergone only these limited toxicity tests but these defects were made up by re-running toxicity tests according to the new guidelines for oral contraceptives that had been set up by the Bureau of Medicine for pre-clinical investigations and clinical studies. The outlines for tests in animals were worked

243
up by the scientists in the then operational Drug Review Branch of the Division of Toxicological Evaluation, Bureau of Science. This organization was responsible for the handling of all matters pertaining to pharmacology and toxicology of new drugs. The scientists responsible for working up the guidelines are specialists in the field of physiology and endocrinology of reproduction, with academic experience in these areas and expertise in hormonal contraceptives. The guidelines under the title “Current Criteria for Evaluation of Progestational Agents and Oral Contraceptives: Preclinical Investigations” were presented to the FDA’s Advisory Committee for Obstetrics and Gynecology in November of 1965. In essence these guidelines did not prescribe “specified” tests but described both pharmacological and toxicological investigations and pointed out those areas needing closer scrutiny for the hormonal functional specificities that would contribute to the contraceptive action of hormonal preparation. Therefore these guidelines cannot be considered to be “specified” toxicity test requirements as set out in the Questions. Many of the aspects that later on were criticized by some were already pointed out then: The possibility of hormonal overstimulation by the higher dose ranges, unavoidable for toxicity assessment, was anticipated to become somewhat of a dilemma when attempting to sort out effects resulting from hormonal hyperactivity from those of a direct or secondary toxic effect. Also, the possibility of complications in dogs arising from the drug being administered in the human cycle regimen which is required for these tests, when superimposed on the seasonally mono-oestrous pattern of the canine was pointed out (but, as was found out by these tests, this did not pose a major problem: the canine proved rather capable of adjusting to this enforced alien regimen!). It was also pointed out that new hormones incorporating changes in their chemical structures deviating from that of their parent compound, had to be considered a new drug, in accordance with the law; therefore their safety status had to be investigated by the prescribed test procedures. The “well known” sensitivity of the canine to oestrogens was anticipated, but this too proved to be an unneeded concern for the oestrogens present in modern contraceptives. There were other items in the guidelines brought to the attention of the investigator, but time does not permit me to go into details. Interestingly enough, there were few, if any, objections from industry concerning the requests in the guidelines; nobody at that time seemed concerned over differences in the metabolism pattern between animals and the human; and there were no objections to the beagle. There were some objections raised from a clinical standpoint because of the longer test periods in animals required for contraceptives as opposed to other drugs in order to support Phase II studies.

These guidelines were just becoming operational when the incidence of MK 665 occurred. As a consequence, the beagle became mandatory as a test animal, and the rhesus monkey was added as a test animal. Furthermore, the com-
pletion of a one year treatment period in rodents, dogs and monkeys became necessary for even limited Phase II studies. Another timewise extension of the animal tests to support the respective clinical phase had to be added when it was observed in the then running toxicity test that mammary nodules were induced in the beagles by some preparations after treatment periods of more than one year, that is nodules did not appear in the first year but did in the second year. The table below presents the present requirements for animal tests for contraceptives of the hormonal type, and also for progestins and oestrogens for prolonged non-contraceptive use.

<table>
<thead>
<tr>
<th>Clinical study</th>
<th>Animal toxicity study requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I (limited to a few subjects for up to 10 days administration)</td>
<td>90-day studies in rats, dogs, and monkeys</td>
</tr>
<tr>
<td>Phase II (approximately 50 subjects for 3 menstrual cycles)</td>
<td>1-year studies in rats, dogs, and monkeys</td>
</tr>
<tr>
<td>Phase III (clinical trial)</td>
<td>2-year studies in rats, dogs, and monkeys.</td>
</tr>
<tr>
<td></td>
<td>Initiation of 7-year dog and 10-year monkey studies prior to start of Phase III</td>
</tr>
<tr>
<td>New Drug Application</td>
<td>No further requirements, but must include up-to-date progress reports on long-term dog and monkey studies</td>
</tr>
</tbody>
</table>

These requirements were prepared by the FDA and, as were their predecessors, were submitted to the FDA's OB/GYN Advisory Committee for their review. They were published in the FDA Papers of November 1969.

It should be noted that they do not apply to oestrogens and progestins used clinically for short periods, e.g. for inhibition of lactation, and they would not apply to oestrogens used for post-coital contraception with restricted frequency of use. Nor would they apply to agents of different hormonal types such as prostaglandins that would work by a similar manner and usage as a once-a-month pill, if they ever materialize. With some modification they apply to hormonal agents carried on IUD’s, depending on the nature of the hormone. By definition of the law, the intrauterine administration of an old progestin would make it a new drug. The Advisory Committee recommended that the intrauterine type of contraceptive be investigated in cycling species, preferable rhesus monkeys, for the local effects of the combination of a physical action
of the IUD with the hormonal action, with treatment periods to extend for at least one year, even with known compounds, to support extended clinical investigations. Depending on the results of these tests, decisions in regard to the need for long range tests will be made later. So far there was no need for guidelines for testing IUD’s carrying drugs other than hormones. These will have to be drawn up in accord with the kind of drug involved. Depending on its properties, chronic studies may become a necessity.

When a few years ago it looked as if prostaglandins in the form of a self-administered vaginal tablet administered once a month would provide the birth control means to end all problems, we drew up a set of guidelines for such preparations. These recommended that the physiology and pharmacology of the prostaglandin used should be worked out first, and that the main concern toxicity-wise should be on the effects on future fertility after frequently induced menstruations and early abortions which at that time appeared feasible. This effect was to be investigated in at least 3 animal species, rat, rabbit and monkey, by midcycle administration for several months or cycles, followed by attempts to produce pregnancies. These guideline are presently in a “resting” stage because no need has developed as yet, but it may arise when prostaglandins suitable for this action materialize. They could be used also for drugs mimicking the prostaglandin action.

The long range studies in beagles and rhesus monkeys with hormonal contraceptives were requested to be conducted by their manufacturers for the purpose of obtaining information of predictive nature on the possibility of complications arising from their use over almost half of a lifetime of the human female. These studies became mandatory in the fall of 1967 because of the tumorigenicity observed from the MK 665 studies even though opposite views also had been expressed that the MK 665 effect in beagles was not unexpected. In the context of this discussion and of the Questions they do qualify to be considered “specified FDA toxicology requirements”, in the meaning of the terminology used in the Questions, in that prospective studies of this nature are required only for hormonal contraceptives but not for other drugs. They are “requirements” in the sense that they must be conducted by manufacturers and developers of preparations of this type according to protocols prepared by the FDA staff in order to obtain marketing approval. They affected, at their start, already marketed products and those in investigational status, and now must be initiated for all formulations as soon as they reach Phase III clinical investigation status.

As mentioned before, expert advice from outside had been sought beforehand, including the FDA’s OB/GYN Advisory Committee in regard to the justification for these investigations and their technical extent and implementation. Since then the Advisory Committee has been kept informed currently on events in these studies, and their opinion has been obtained in every instance
when regulatory actions by the agency appeared necessary because of adverse developments. In one instance, a special ad-hoc committee of experts was convened to help in the resolution of questions of the significance of results with one of the formulations. Final decisions were and are made on the very top level of the agency.

The selection of the most suitable animal species to provide meaningful results was a serious dilemma then, and obviously it still exists today, or else there would not have been a good cause to convene this conference. An animal species totally resembling the human species to make it unequivocally suitable for tests of this sort, or for any kind of test procedure for that matter, just has not been created. For these compounds, rodents, conventionally used for carcinogen assays, did not seem to fill the need for a representative animal model. Therefore, the two species now required to be used in the tests seemed a logical choice not only because of their history in the MK 665 affair, but also because of the experience from their use in the toxicology tests. It was a logical and practical approach and is still unchallengeable on grounds of science. Note that the rodent is still a required species by the FDA, but the dog and monkey have been added.

The dosages of 10 and 25 times the anticipated human dose for the dog studies, and 10 and 50 times for the monkey study were advised by specialists in the cancer research field but admittedly the high doses may cause anguish to an endocrinologist. The reduced high dose in the dog study was a concession to demands by the industry because it was taken for granted that the canine would not be able to survive long enough to bring out a carcinogenic potential. For the same reason the prescribed treatment period of 7 years for the dog study was arrived at in consideration that this period would represent a half lifespan and would be long enough to extend treatment into the age when spontaneous mammary tumours are believed to appear.

The low dose of 1 or 2 times the human dose was not mandatory but those who did choose to add this dosage, probably made a wise decision, especially for those compounds that at the higher dosages did induce adverse reactions in the mammary area.

In those cases where a manufacturer had several formulations with the same agents but in various ratios, he was given the choice which of these to use in the tests as long as the difference in the ratios did not alter the endocrinological spectrum of the formulation to a marked degree. This assurance had to be established by appropriate pharmacological investigations. This policy is still followed and applies to new formulations.

The number of animals per dose group was minimally 12, but most carried 16–20. This number was recommended to us as being sufficient for statistical significance. Large numbers would have made the cost prohibitive. Twenty-six
studies were started in each species and some of them are now in progress for over 6 years.

Now we come to the question of crucial significance: "How successful have these requirements been and by what criteria?"

This needs a little philosophising first. What are criteria for a successful toxicity test? The answer is simple for compounds when their toxicity tests in animals indicate a low order of toxicity and when, because of the low risk involved, that particular drug is put on clinical trials and no toxic effects are induced in the human. With drugs of the nature of the oral contraceptives the problem becomes much more complex because of the involvement of the carcinogenic potential with its needed long exposure time in the human. Therefore a valid comparison between the outcome of the animal tests and the human clinical experience is not possible. It becomes even more complicated when adverse effects do show up in the animal test that are interpreted to be sufficiently serious to not allow administration to humans for clinical tests. In these cases immediately the issue is raised of the significance of the animal test results for their extrapolation to the human, and indeed the possibility may arise that a drug of potential value is deprived of its chance. It is appropriate to state, at this time, that those who raised a "hue and cry" about the question-ability of attempting to extrapolate animal findings to the humans when adverse effects appear in animals, are silent on the subject when no adverse effects are observed in animals. Is there a way to eliminate the undesirable situation of an important new drug being lost to the public? Would it be ethically justifiable to take the risk and to test the suspicious drug anyway to find out whether or not it has the desired, possibly even a superior, therapeutic action?

There is no question that such risk is justifiable for drugs that are used to treat certain diseases and indeed, FDA and other regulatory agencies have permitted investigation and marketing of drugs found to be tumorigenic in the animals. But is this risk justifiable for oral contraceptives, particularly where a therapeutic advantage has not been established clinically?

In our search to obtain aid for our interpretations of results in the contraceptive studies for carcinogenicity, we were given by the staff members of the National Cancer Institute the following definitions that have merit but still do not provide a "formula" to measure drug toxicity nor carcinogenicity:

"Safety" is defined as the practical certainty that injury will not result from the substance when used in the quantity and in the manner proposed for its use.

"Hazard" is the probability that injury will result from the use of a substance in a proposed quantity and manner.

"Acceptable Risk Dose" is that which causes no more than the arbitrarily allowed acceptable risk.
“Social Selection of Acceptable Risk” is based on the information available on the consequences of accepting a given risk and the projected benefits that would result.

These definitions are certainly interesting for their philosophy but do they really give much help and comfort to a pharmacologist-reviewer pondering over some toxicity test data in an IND, in this endeavour to arrive at a decision that may or may not lead to a regulatory action?

With these reservations and considerations in mind, we offer these points for the evaluation of the successful application of the FDA requirements of toxicity testing of contraceptive products:

The American Consumer and the medical profession have at their disposal oral contraceptives that can be considered safe and effective according to the state of the art, the principles of toxicology and the laws of the country. They were approved for use by the Food and Drug Administration after they had passed the toxicity tests prescribed for these drugs, namely, the chronic toxicity tests in three species, the rat, dog, and monkey, some additionally also in a fourth species, the mouse, without disclosing properties interpretable as being hazardous to the human. These contraceptive drugs are presently on the prescribed long range tests in beagles and rhesus monkeys designed as prospective studies to disclose carcinogenic potentials affecting the mammary gland. These formulations have not disclosed a tumorigenic or carcinogenic potential affecting the human breast. These products are combinations of norethindrone or its derivatives with either ethinyl oestradiol or mestranol. The majority of them are for cyclic administration, one is for the sequential regimen, and one is a microdose compound containing only norethindrone. One other microdose compound containing norgestrel has just been approved. The latter two have as yet shorter use periods to their credit, than most of the others. Thus, for these types of contraceptive products there exists a close correlation between their actions toxic-wise, in the animal test model and the human. This agreement between the activities of these contraceptives in four animal species and the human speaks for the efficacy of the FDA requirements.

It has to be stated that some nodules have been induced by these compounds in beagles but with a low order of incidence, often lower than in the control animals, both with respect to numbers of animals and numbers of nodules. There is some fluctuation in the occurrence of nodules even in the high dose groups, almost of a seasonal periodicity, a puzzling phenomenon. It remains to be seen if a trend will develop towards an increase in nodules with advancing age of the animals.

Another example of the effectivity of the FDA requirements for the protection of the human from exposure to possibly hazardous drugs is the experience with several investigational contraceptives whose toxic potential was uncovered by the provision in the toxicity test requirement that new compounds
must be investigated for one year in 3 species, in order to support Phase II clinical investigations in a restricted number of patients for a treatment period of only 3 cycles. Compounds were submitted to FDA for evaluation of preclinical data that clearly indicated a highly hazardous nature of the compound, yet the sponsors apparently had intended to proceed with clinical investigations. There were cases when unpredictably high cataractogenic action was seen in rats; hepatotoxic effects in monkeys and rats; excessive endometrial hyperplasia in monkeys bordering on malignancy; more than the usually encountered pituitary changes in rats and mice, and pronounced carcinogenicity in the mammary glands in rats, just to mention a few. Since none of these compounds seemed to possess any advantages in clinical utility over already existing compounds, so far as could be judged from their endocrinological properties shown in the pharmacological tests in animals, their administration to the human was prevented. These decisions in general were and are made on a divisional level without any complication. In instances of drugs that indicate a superior property more elaborate steps are taken by the agency to assess the benefit-to-risk ratio, involving our Advisory Committee and, on occasion, ad-hoc panels of experts, and consultants, such as pathologists. It must be stated that in recent years it has not happened too frequently that a completely hopeless compound was brought before us.

Under the old regulations, though, before introduction of the specified requirements for contraceptives, in force now since 1967 and 1969, obviously hazardous compounds would have been administered to more people before their hazardous nature had been realized, and under the conditions existing before the enactment of Kefauver-Harris Amendments, many more people could have been exposed to them without FDA ever hearing of it, and a follow-up of the patients would not have been possible.

It is probably significant that most of the compounds with the described adverse effects in the animal model are derivatives of norethindrone with minor and major chemical alterations in the molecule which obviously were introduced for the intended purpose of improving the functional qualities of the new form. It cannot be deduced from the animal tests whether or not these goals were achieved, but it almost looks as if the further the chemical alterations removed the compound from the original parent compound norethindrone, the less desirable its actions became.

The chemical configuration appears to play a significant role in the expression of the carcinogenic or at least tumorigenic potential of the derivatives. MK 665 is a chloro-ethynyl norethindrone, and is definitely tumorigenic, at least in the beagle. The chloro-ethynyl group introduced to the innocuous norgestrel molecule makes it highly tumorigenic, and probably not by increasing its progestagenic potency alone. The same change in mestranol is said to increase its carcinogenic action in the responsive rodent.

250
Returning to the issue of assessing the success of the FDA toxicity test requirements, these came under fire of international extent when the agency saw a need for action in the case of chlormadinone acetate. The wide unfavourable reaction to this step by FDA was stirred up by the fact that this progestogen had been expected to be the “Pill Without Problems”: it was the prototype of the spectacular microdose, the simple continuous administration regime, it was a pure progestagen hypothetically safe from thromboembolic complications, and it was supposed to work as an effective contraceptive through its “luteal supplementation” principle without affecting the pituitary-ovarian axis, with no effect on the menstrual pattern. And then along comes the FDA and deprives the people of these “advantages” just because of some nodules in beagles! Actually by the time the nodules had appeared in the dogs, after a shorter treatment period than needed for other compounds at that, it had already become apparent that the luteal supplementation principle did not live up to expectations, that it did not work uniformly in all users, that its contraceptive efficacy was lower than for the approved cyclic combination O.C.’s, that ovulation is inhibited in about one third of the users and that menstrual rhythmicity is displaced by irregular bleeding episodes. Some of the nodules found in beagles were diagnosed by about half of the pathologists inspecting them as being already premalignant. Consultations on regulatory and scientific actions took place at the highest level of the agency, with the FDA Advisory Committee, and with a special ad-hoc panel of specialists. The benefit-to-risk ratio was not in favour of this product, under domestic conditions.

The main arguments against the FDA decision are based on the difference in the metabolism between the human and the dog, and on the claim that the dog system is more susceptible to progestagenic impulses than the human. It would lead beyond the scope of this discussion to dispute these aspects. There is reason to believe that for this compound too its chemical configuration is connected with its carcinogenic action in the beagles.

Furthermore, it has come to our attention that an analogue of this drug is apt to induce nodules in the breast of human males. All this put together makes the decision on chlormadinone acetate reached by FDA justified for the condition in the U. S.

A different stand was taken by the agency in the case of the depot-injectable preparation of medroxyprogesterone acetate. Even though this compound too is implicated by its action in beagles as being potentially carcinogenic, the uniqueness of this preparation and its high efficacy as a contraceptive, no matter by which pathway this contraceptive effect is obtained, provides it with a benefit-risk ratio which permits its use in the U. S. albeit for a very special patient population. Although the criteria for patient selection will make its use limited in the U. S., these criteria may have more widespread applicability in other countries.

251
In the case of the orally administered combination product containing medroxyprogesterone acetate with ethynyl oestradiol, however, there being no clinical advantage of this product over other combinations, it was removed from the market because of the beagle findings with depot medroxyprogesterone acetate.

In conclusion, we feel that there is no reason of value to disregard the results obtained in the beagle studies for the tumorigenic or carcinogenic potential of hormonal contraceptives, nor to remove the beagle as a test animal for the prospective investigations. We do not feel at this time that the difference in the metabolism pattern between the human and the canine is an uncontradictable argument against the use of the canine species. And what of the difference in the metabolism between the rodent and the human, and the monkey and the human? Why isn't a question raised about unsuitability of these species?

We feel that the experience with FDA toxicity test requirements has proven their value for the protection of the American user of contraceptive preparations of the hormonal type. This statement is not meant to imply that the tumorigenicity of certain compounds demonstrated in the beagle can be extrapolated to the human, but the negative data obtained with those compounds we have permitted to be marketed has given us a certain measure of assurance, and the positive data on toxic effects unrelated to tumorigenicity have prevented human exposure to these compounds.

In the light of new developments in the field of fertility regulation utilizing the much more refined and highly sophisticated methodologies and instrumentation not available only a few years back, it now seems justified to regard the entire issue of the presently available hormonal contraceptive products from a retrospective, already historical angle and viewpoint, including their toxicity test requirements, and their implementation in the past and to-day. These contraceptive products have probably reached their peak and summit, both development and use-wise, they have played their significant role in the introduction of the new era of birth control, and they will continue to do so far sometime to come yet, but there are indications that the future will bring forth new drugs providing different approaches and acting in new and more accurately established pathways and systems. For them the existing methodologies of toxicology testing that helped to bring out the pioneer products of today no longer will be usable and applicable. The FDA is preparing for this development by implementing the expanded utilisation of existing advisory committees, and the formation of a new Advisory Committee for Toxicology and Pharmacology that in the future will participate in the formulation of guidelines for test procedures and the evaluation of test results. Already in existence, in the effort in the direction towards greater participation by industry, are the recently established committees with representatives from industry and FDA
working together on writing new guidelines for all drug classes to bring them in line with new developments in science and the state of the art. Thus, while in the past, in the area of contraceptive drugs there had not been a definite mechanism within the FDA to draw up requirements for toxicity and other tests, and for their evaluation, except for consultations with the advisory committees described in this discussion, the contemplated organizations will provide this mechanism needed in view of the ever increasing complexities of drug actions and interactions.

In closing, it must be reminded that the foregoing presentation was made on request to describe facts and background information for FDA activities and policies in the outlined area, without any intent of recommending their acceptance for different conditions and circumstances. The benefit-to-risk principle alone is bound to vary from country to country requiring variations in interpretations of results obtained in tests for toxicity, carcinogenicity and other multi-phased complexities arising from such investigations. Different interpretations and their consequent utilization by different agencies in different countries must be mutually treated with respect and understanding, sometimes even with compassion, and decisions must be made by the responsible agencies on their merits for prevailing conditions and in the best public interest.