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Comments on Biotechnology Draft Document, 2/27/92

-What has happened to the scientific elements of this document? Without a sound scientific base to rest on, this becomes a broad, general, "What do I have to do to avoid trouble"-type document. The examples do not supply the scientific rational that is needed. A scientific document is needed, because there is very little (even when things are called scientific) scientific information supplied. If the FDA wants to have a document based upon scientific principles these principles must be included, otherwise it will look like and probably be just a political document.

-This document reads like a biotech REDBOOK!! The initial intent of the document was to present scientific considerations and to avoid telling industry what tests to run and how to go about doing it, but the flow charts do just what (initially) was to be avoided.

-It reads very pro-industry, especially in the area of unintended effects, but contains very little input from consumers and only a few answers for their concerns, many of which would be answered by supplying the scientific grounding principles.

-The document is inconsistent, in that it says (implies) that there are no differences between traditional breeding and recombinant, yet consultations, and premarket approvals are being bantered around, when they have not been used for foods before. In fact the FDA is making a distinction, so why pretend otherwise.

-The unintended effects cannot be written off so easily by just implying that they too occur in traditional breeding. There is a profound difference between the types of unexpected effects from traditional breeding and genetic engineering which is just glanced over in this document. This is not to say that they are more dangerous, just quite different, and this difference should be and is not addressed.

-A lot of time is spent on selectable markers, which in reality will not be of much concern with the advent of several ways to disarm the marker gene. If the length of the section is any indication of the level of concern, then this is way out of proportion.

-The flow charts are just a version of the Redbook, hoops through which industry must jump, and not scientific considerations. Industry will do what it HAS to do to satisfy the FDA "requirements" and not do the tests that they would normally do because they are not on the FDA's list.

-Why should companies conduct tests as described in the flow charts if there are no differences between traditional foods and those produced by modern technology? And what are the regulatory grounds for all the "shoulds" that are spread throughout this document? If industry does not follow these "should" items is the FDA going to perform these tests and penalize the companies or does the Agency wait for something to go wrong and then act?

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Specific Comments

-pg.3, line 24 (and elsewhere)- How many "first" examples will

have to be examined? First examples of what- new genes; new types of modifications; genes from organisms from other kingdoms; first submissions? Also in order not to be sued by the "first" group of submitting biotech companies who will be required to submit data when others later on will not, what will they receive for being the guinea pigs? (After all even those who do not submit will also have the implicit seal of approval from the FDA if the "follow" the code of practice.)

-pg.6- (In order to bolster the idea of a scientific basis for this document) please add something like this to line 4: "...these and other documents, including scientific research in developing this notice."

-pg.7, line 12- "...notice also discusses in detail current..." Where is the detailed scientific discussions? This sentence has to be revised considering that there are few really scientific details presented.

-pg.7, line 14-17- The scientific considerations are NOT the Codes of Practice. The scientific considerations are ideas which can be discussed (proved or disproved). The Codes of Practice are guidelines (hoops) for industry to follow. They will not want to discuss them scientifically since they will be viewed as the FDA Guidelines for Plant Biotechnology. (Page 36, lines 10-12, "The Codes of Practice identify specific situations where developers should consult with FDA.") These sound like practical (regulatory), not scientific concerns.

-pg.7, line 18- "First" examples again, who decides when enough is enough? Industry? FDA? Congress? Safety? The President? The Council for Competitiveness?

-pg.7, line 24-...will not be challenged on legal grounds... If there is no difference between traditional foods and genetically engineered foods, then why would the FDA even bother to challenge them; unless it is really saying that they are in fact different.

-pg.8, lines 9-10- Has any other whole food ever needed pre-market approval? If not, then this is saying that the two ways of producing foods are in fact different.

-pg.11, line 16- "Wide" crosses are defined as NOT between closely related species or genera.

-pg.12, lines 20-23- Is it really feasible to think that breeders would freely (without some sort of urging) backcross to get only one chromosomal location, unless there was interference with the desired outcome. And besides multiple copies inserted at one site could become potential sites for rearrangements, especially if used in future gene transfer experiments, and as such may be more hazardous.

-pg.13, lines 10-12- If the idea of this sentence is to reassure people that this process will require many crosses as a kind of fail-safe system, it will fail. There are already techniques available that will transform formally hard to transform "elite" lines. When these are used, there will be less backcrossing, and therefore not as much concern about safety.

-pg.13, lines 13-16- One viewpoint is that once the technology really catches on, that there will be less site-years put into

products, rather than more. This will mean less concern about safety, because of a false sense of "knowing what one is doing" and "its been done hundreds of times before without a problem, why check it now".

-pg.15-16, Unexpected Effects- This is industry's pet idea, namely that there are no unintended effects that will raise the FDA's level of concern. But time and time again, there is no data to backup their contention, while the scientific literature does contain many examples of naturally occurring pleiotropic effects. When the introduction of genes into plant's genome randomly occurs, as is the case with the current technology (but not traditional breeding), it seems apparent that many pleiotropic effects will occur. Many of these effects might not be seen by the breeder because of the more or less similar growing conditions in the limited trials that are performed. Until more of these experimental plants have a wider environmental distribution, it would be premature for the FDA to summarily dismiss pleiotropy as is done here.

-pg.38, line 8- "FDA has also been asked whether foods developed by with... (delete the word with).

-pg.42, lines 1-4- The potential for activating cryptic pathways has NOT "been effectively managed in the past by sound agricultural practices", because the breeders have not had to face the issue of new, powerful regulatory elements being randomly inserted into the genome. So there is no certainty that they will be able to pick up effects that might not be obvious, such as cryptic pathway activation. This situation IS different than that experienced by traditional breeding techniques.

-pg.45, Chart II, box that reads- "Is the host plant or related species a source of toxicants?" All plants produce toxicants, so the answer to this question is always YES. Many of these toxicants are directed against insects or other herbivores, and so there is little knowledge as to their effect on humans. At their native dose ranges, they might be benign, but if they are increased by unintended effects, their effect(s) are unknown. So to just say "No problem" would be premature and potentially unsafe.

-pg.46, Chart III, box that reads- "Is there clear evidence that allergens have not been transferred to host?" Since there are very few allergens that have been identified at the protein or gene level, this question can only be answered "No" when the gene comes from a plant which produces allergies. So the companies are going to have to consult FDA on tomatoes, peanuts, wheat, and every other plant which produces allergic reactions. Also the only definitive test for allergies is human consumption by affected peoples, which can have ethical considerations.

-pg.46, Chart III, box that reads- Donor a source of toxic substances? SEE ANSWER TO pg.45, Chart II.

-pg.46, Chart III, box that reads- "Evidence that the donor toxic..." Donor should read DONOR'S.

-pg.47, Chart IV, box that reads- "Newly introduced protein present in food from the plant?" This does not take into account, nor does the document as a whole, those introduced proteins

(enzymes) that while acting on one specific, intended substrate to produce a desired effect, will also affect other cellular molecules, either as substrates, or by swamping the plant's regulatory/metabolic system and depriving the plant of resources needed for other things. It is not prudent to rely on plant breeders always finding these types of changes (especially when they are under pressure to get a product out). No where is such an issue discussed or examined in this document.

-pg.47, Chart IV, box that reads- "Will the donor...processing in donor?" Since there are several possible answers for this one question coming from several sources, it should be split up into two separate questions. The first question should end with "...to levels in donor or other food?" and the second question (separate box) Should begin "Will the processing in new...?".

-pg.47, Chart IV, box that reads- "Will the introduced protein be a macroconstituent, or have a cumulative exposure due to use in many foods?" Should this read, "...or have an increased cumulative exposure..."?

-pg.48, Chart V, box that reads- "Has there been an intentional alteration...", what about **UNINTENTIONAL** alteration? These can and do occur, and could affect the food in subtle ways, that might not be picked up by traditional plant breeders, unless of course they are using biochemical carbohydrate testing procedures.

-pg.48, Chart V, box that reads- "Have any structure...that do not normally occur in carbohydrates?" The strict answer to this question all the time is "NO" because unless some brand new carbo combination is invented by the plant, any combination can be found in some organism somewhere on earth. Maybe it should read, "...that do not normally occur in food carbohydrates?"

-pg.48, Chart V, boxes that reads- "Consult the FDA", these two boxes should be made into one, because it would be more beneficial to the companies to consult after they have completely analyzed the product than after piecemeal analysis. It would be less work for the agency as well.

-pg.49, Chart VI, box that reads- "Is there a significantly altered ratio of omega-6 to omega-3 fatty acids?" Is this the only fatty acid ratio that the FDA will be concerned about, and what happens if this ratio is shown to be non-significant? "Ratios of critical fatty acids, ought to be examined.", might be a way around this problem.

-pg.56-57, lines beginning at 15 and ending on 5- This is a repeat of the material under the section called "a. Whole plants" on page 55, and it does not belong. There is much more appropriate material that should go here.

-pg.66, lines 12-16- If individual proteins are produced in significant quantities, so what. The document just stated in the line above (5-7) that "...the amount and quality of total protein in the diet, rather than of any particular protein, is of greatest significance." The logical reason for the statement beginning on line 12 is not obvious.

-pg.74, line 10 onward- The Toxicology section is going to be a problem. Industry will say it is too much and the

environmental/consumer groups will say it is not enough. A more complete presentation of the scientific concerns than is given in this document, as well as a more forceful show of reliance on the usefulness of molecular biology would have reduced this problem by spelling out the need for toxicity tests in limited circumstances. Better yet, a separate (Federal Register) presentation of the scientific concerns with an analysis of comments before ever producing flow charts of guidelines (as currently presented) would produce better understood guidelines.

-pg.78- This environmental section is quite important, but it should be separate or at least given a different label that indicates that it is separate. It could be shortened by being less wordy, without diminishing it's importance.

-pg.78, lines 20-25- "It may be reasonable...plant species into the ecosystem." A recent report in the Feb. 8, 1992 issue of New Scientist (pg.40-44), by C. Heron, implies that plants can form hybrid chains that include plants that are not often considered capable of making such hybrids. There are many things about hybridization that are not known that could cause the transfer of introduced genes into unintended species. This possibility should not be written off so easily.

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