of drugs which are perhaps unlikely to have a bioavailability problem than it is those which are likely to. And in general, the water-soluble compounds and those which go into solution readily in the stomach, do not have bioavailability problems.

I would like to, as a general principle, state something that I think has caused a lot of confusion. There are two issues that I think are being mixed up at the moment by a number of people; and they should not be mixed up for us to properly consider public policy.

One issue is are there lots of examples of a drug in different dosage forms, in different crystal sizes, and so on, and different salts, which produce different blood levels? The answer to that is yes. There is an enormously expanding literature to the effect that the same active molecule, if you compound it differently and put it in the form of a different salt, if you put it with different binders in a tablet and so on, that you may get different blood levels. Now, that is being done purposefully by people in biopharmaceutics who are experts, for the purpose of identifying the principles of how to compound a good tablet.

Now, you cannot mix that literature up with another problem. The other problem is: If there are already well-known standards for the manufacture of a drug, and if two manufacturers are trying to make the identical thing, absolutely identical—same salt, same dosage size, same tablet, everything—how often—excuse me—and the products they make meets all the compendium standards, how many examples are there then that unsuspectingly those two products were different?

Now, that is the issue in public policy. And that is the short list which the Commissioner just gave you.

Now, I think there are some—they include both the Pharmaceutical Manufacturers Association and the Academy of Pharmaceutical Sciences—who are tending to mix up those two issues and tending to take the large literature, demonstrating a lot of differences between drugs when they are in slightly different dosage forms, and say that is relevant to the second issue, which is two manufacturers trying hard to make a drug, and they both meet identical standards. And those should not be mixed up.

I want to make it very clear, because otherwise the list we gave you is subject to attack. But we do not think it is subject to attack if the attackers will stick by the ground rules we just gave you—namely, identical product, identical salt, made by—all meeting compendium standards, and the difference between them is unsuspected.

Senator NELSON. Is there not a further question, and that concerns a drug that achieves a different blood level at a different rate, but that this difference has no therapeutic significance.

Dr. CROUT. Yes. That is possible; indeed, it happens all of the time. And that is a matter then of judgment on whether these two different forms are identical. But that is a judgment of man that applies to all issues, if you will, and indeed, to all drug issues besides bioavailability.

We have to make those kinds of judgments, for instance, on clinical data or on efficacy also.