Rec'd 9/18/98 b

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September 16, 1998

Jane Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike, Room 6027
Rockville, Maryland 20852

RE: FDA Modernization Act 1997. Compounding Provision.

Dear Jane:

Please find enclosed material for the docket (I believe 98D-0272). I request that this material be put on the internet.

Sincerely,

John H. Perrin

John H. Perrin, Ph.D.
Professor of Medicinal Chemistry

Cc: Rep Karen Thurman

98D-0272

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Comments on Drugs Difficult to Compound and the Quality of Chemicals to be used in Compounding.

J.H. Perrin, Ph.D.
Professor of Medicinal Chemistry
University of Florida

1.SUSTAINED RELEASE PRODUCTS

These should never be compounded. I have recently read that it takes companies whose business is solely the design of sustained release oral products, five to seven years to successfully develop a new product, the longer time being necessary for the more water soluble molecules.

They why can a compounding pharmacist make any drug into a sustained release product regardless of water solubility, pharmaco kinetic parameters etc from a general formula provided by a supply company in ten minutes? Mixing with hydroxymethyl cellulose or related substance and lactose and placing in a capsule is the prefered method with no testing of total drug content or rate of dissolution. The commonest drugs sold by compounding pharmacists in this way are morphine sulfate, oxycodone hydrochloride and verapramil, although theophylline a drug on many negative formularies has been compounded. I have already written that such sustained release products can be expected to release the active ingredient far too quickly and may not release all the active ingredient in the end. This has been confirmed in data for verapramil sent to my graduate student from a pharmacy school, receiving support from a supply company, which teaches students how to compound sustained release capsules and determines their dissolution characteristics. This data also confirmed

what had been reported on national television using data obtained in the commercial laboratory regarded as the leaders in evaluating sustained release products. I know of two pharmacies that make sustained release methylphenidate capsules. Parents have told me that they can tell how much water their child has consumed by the behavior of the child. Isn't this also predictable? Of course, that the release of the active ingredient from a manufactured sustained release product must be independent of food and water intake is never mentioned at the cult meetings of compounding pharmacists. They were also making sustained release Fen Phen products with both drugs in the same capsule. Of course the main target of compounding pharmacists is the vulnerable elderly in the form of sales of sustained release morphine and oxycodone to nursing homes hospices etc in the Sun Belt. These sales result in huge profits for the nursing homes and compounding pharmacists, helped by the overpricing by the legitimate manufacturer. In any other industrialized nation and in most of the third world, pharmacists making their own sustained release products would lose their license for life, in the US they become leaders of the profession. Compounding pharmacists also make slow release estrogen implants. No slow release product should ever be compounded.

PRODUCTS MANUFACTURED TO BE RECONSTITUTED BY THE PHARMACIST

Here we have mostly pediatric suspensions and injections. It costs the manufacturer much more to produce these products for reconstitution than it would if they sold a finished drug. So, compounders, there must be a reason for the sale of product to be reconstructed, it is stability, something which you totally ignore. The

worst case is probably Augmentin. The pH profile of molecules are never looked at by compounding pharmacists, the patient's parent is simply asked what is the child's favorite flavor. I have had calls from parents who have had several products reflavored and their child has become very sick. The child has recovered when the original drug was correctly reconstituted in a chain pharmacy. A sample of one proves nothing but any thoughtful pharmacist should see a red flag when reconstitution is involved. The matter is not simply one of pH, as has been stated to compounders, but also involves potential catalysis by all added components and most importantly of all the solubility of the hydrolysable molecule, the solubility also being influenced by pH and the presence of all other ingredients. In some compounding pharmacies seats are provided for children to watch their medicine being made or perhaps mutilated. No active ingredient supplied in a form to be reconstituted, should ever be involved in the preparation of another liquid dosage form.

INJECTABLES

By law injectables should be sterile and pyrogen free. The Millipore filters and generic equivalents used by compounding pharmacists are excellent for helping maintain sterility during transfer of one sterile solution to another, they are not designed as a primary method of sterilization and they do not remove pyrogens. Of the several injections made by compounding pharmacies the worst example is morphine sulfate for intrathecal use sometimes with the addition of clonidine. It is well documented that the spinal fluid is very much more susceptible to pyrogens than is the blood. Why is this popular I have been told by a very reliable person that if

someone knowingly takes advantage of loopholes in medicare payments methods then they are guilty of medicare fraud. Thus medicare fraud is the reason for compounders making morphine sulfate injections for intrathecal use. The Merck Index gives a water solubility of morphine sulfate as around 64 mg per ml at room temperature. A commercial product, ie one proved to be sterile and pyrogen free, of 50 mg per ml is available. There is absolutely no need to compound these products other than to take advantage of the ridiculous amount paid by medicare for the compounding of morphine sulfate injection. You can read how to make these injections in an early issue of the International Journal of Pharmaceutical Compounding. No analysis of the finished product is recommended in the article but occasional testing of sterility and freedom from pyrogens. This journal accepts advertising from supply companies, I have been told that the editor has been involved with a supply company for years, and he is supposedly representing the USP on this committee. A major, major, major conflict of interest I think, but apparently not in the eyes of the FDA or USP. There is need to make injections very occasionally in an institutional setting, but these should never be released until tested for sterility and pyrogens as well as undergoing chemical analysis. It is criminal to make injections for intrathecal use without testing for at least pyrogens and sterility. Testing drugs, by using caveman type technology, ie using five senses as suggested by a prominent member of the Florida affiliate of the American Pharmaceutical Association on national television is hardly adequate as we approach the third millenium.

INHALATION FLUIDS

I personally would only use a sterile inhalation fluid provided in a sealed unit dose container. The active ingredients of inhalation fluids are notoriously fragile molecules. Their decomposition can be accelerated by filter materials, plastic, glass and metals used during production. Every new supply of filter materials container materials has to be tested by the manufacturer for compatibility with each active ingredient and any preservative to be added. One type of cheap container cannot be used for all inhalations fluids, as is done by compounding pharmacists. I have been told by students, of benzalkanium solutions being produced in plastic milk cartons in a pharmacy making 30,000 vials a day. Apparently no one considers that the surface active benzalkonium can remove plasticisers from the carton. They also used albuterol manufactured in a third world country and already yellowing. Using chemicals manufactured in third world countries and of unknown quality is common in compound pharmacies. Mixing two active ingredients is not a good idea. For example I have a patient talking to me about a mixture of ipratropium and albuterol containing benzalkonium. A medicaid patient. At first she used commercial products , ie separate active ingredients in sealed vials (the best). Then she was persuaded to have the prescription compounded in a single vial, benzalkonium being added. This very sick patient now found that the interval between doses was shortened considerably, and what once was a prescription for a month now left her several days short. On returning to the original chain pharmacy and obtaining the manufactured separate drugs, the problem disappeared. The potency was thus reduced in the compounded mixture. This is not due to any pharmacological activity

of benzalkonium a problem which has been overstated. The problem is due to poor weighing or stability, probably the latter. Others have told me and will publish information that their laboratories has found a loss of potency in the mixture of albuterol and iprotropium when certain benzalkoniums are added. This can occur even if all three ingredients are of USP quality. Which emphases the point that the USP allows considerable range of ingredients in the mixture called benzalkonium, manufacturers carefully screen every batch of benzalkonium to see if it satisfies the problems in their particular environment. Clinical pharmacy and physician specialists using inhalation fluids have told me that they see no reason to compound inhalation fluids as the proven manufactured products are adequate. Why are they compounded? Again, medicare fraud. Some pharmacies make as many as 100,000 vials a day using 1940's techniques for the delicate molecules of the 1990's. This proves they are compounding not manufacturing. Again the ridiculous fees paid for compounded inhalation fluids by HCFA are the reason for the compounding. Many pharmacies receive several million dollars a year from HCFA for compounded inhalation fluids. It seems to amount to over half a billion dollars a year, nationally. The figures are in the public domain and make interesting reading, many prominent pharmacists i.e. big shots in the state affiliates of the American Pharmaceutical Association are involved. All inhalation fluids should be sterile, the FDA is dragging its heels on this issue following pressure from the leading manufacturer who uses outdated containers. There is absolutely no reason to compound inhalation fluids. We read of the increased treatment of asthma at emergency rooms. Is it not possible

that this is associated with the increased usage of homemade inhalation fluids of unproven quality?

COPYING OF COMMERCIAL PRODUCTS

Compounders have long ignored patents, orphan drugs statuses etc. This must be stopped. Excuses like, the child must be allergic to an ingredient are just excuses to compound. There is absolutely no literature to support these statements and of course no tests are ever conducted on the patient. The copying of commercial products is not allowed in any other industrialized nation and must be stopped in the US.

Before Viagra, we had a prostaglandin injection. Caverject was a protected product but was copied immediately by compounding pharmacists who shipped prefilled syringes and multidose vials around the country. There were many complaints about ineffectiveness and of the subsequent prescription being of different potency than the first. Much of the active ingredient was made in the Czech Republic and was of unproven quality. Why did the FDA take no action against the supply companies providing the prostaglandin or the pharmacies shipping their products around the country? Why did the state boards of pharmacy totally ignore the problem?

OTHER

Currently there is a growing business of compounding mixed estrogens, the composition apparently being frequently determined by the pharmacist. The patients are told that the components are natural, I think they are synthetic or at least seminsynthetic. These are molecules which have limited water solubility and some skill in the formulation of these products is necessary to obtain an adequate dissolution rate. You can read how to make these products is an issue of the International Journal of Pharmaceutical Compounding, no dissolution or stability data is included.

Antibiotics should only be sold as supplied by the manufacturer, ie as the original dosage form on as prepared following the manufacturer's instructions for reconstitution.

Reflavoring should not be done, not only for stability reasons mentioned above but also for safety reasons. There is a great danger of cross contamination in the working conditions of a compounding pharmacy, I do not imagine any have a room dedicated to working with a single antibiotic. I believe that pharmacies are exempt OSHA rules for legitimate reconstitution, but once manipulation of the antibiotic starts, whether for a capsule, a crushed tablet on the powder for reconstitution then OSHA rules apply. Manipulation of antibiotics must be stopped. I believe that pharmacists have contributed to what has been interpreted in a given microenvironment as bacterial resistance, the possibility that the local pharmacist has destroyed the antibiotic never being considered.

As in the other cases the compounding pharmacist hides behind expression like, individualized doses, practicing pharmaceutical care and being part of the triad. Does the compounding pharmacist ever tell the patient and physician that the product has not been tested for quality or performance and if the active ingredients have been manufactured in a third world country? Just what does individualized dosing mean: for example 18.5mg sustained release methylphenidate? What appropriate measurements are made to determine this dose? Do all compounders just observe the patient like the pharmacist from Oklahoma seen on television?

QUALITY OF CHEMICALS USED IN COMPOUNDING

The USP monograph on compounding is embarrassing, the worst section being on quality of chemicals used. No pharmacist is trained to make judgement on the quality of chemicals to be used in drugs. I suspect only two members of this committee one an internationally respected technologist and the other a practicing pharmacists have the necessary experience to make these judgements. To suggest that buying a chemical from a chemical supply company is satisfactory is nonsense, experience has taught me that the impurities are invariably not the same and certainly not in the same concentrations as the form sold for the manufacture of drugs. The certificate of analysis suggestion is also stupid. Just what does a certificate of analysis originating with a minor, non approved company, in a third world country mean? Nothing. Representatives of supply companies have been heard to say we check the melting point and run an infrared on all our chemicals. This is meaningless and shows a complete lack of understanding of the problem. Incidentally, certificates of analysis can be purchased for any chemical off the internet, I suspect compounding

pharmacists are or will be the main clients for this service. The Quality of chemicals to be used to make drugs must be as accepted in the original NDA unless legally modified. USP specifications are no longer satisfactory.

CONCLUSIONS

Sustained release products and inhalation fluids should never be compounded. Injections should only be prepared in an institutional environment and only in extenuating circumstances. Before release they should be assayed for content and pass sterility and pyrogen tests. Active ingredients supplied in forms for reconstitution should never be reformulated. A new set of standards or improved USP monographs must be produced to in order to stop the use of low quality of ingredients in drugs. Technology has been downplayed in pharmacy schools for the last twenty five years, we are not training pharmacists to make value judgements on what can and cannot be compounded, and yet compounding is the fastest growing branch of the profession. We certainly do not train pharmacists to make value judgements in the quality of chemicals used in the preparation of drugs. The US public has been very poorly served by the FDA and the Boards of Pharmacy, the FDA has had the information necessary to stop the supply questionable quality chemicals and of unproven drugs, but has taken no action. Why? Even worse is the situation in the states with the Boards of Pharmacy. The boards seem intimidated by compounding pharmacists the supply companies and the politicians supporting both. Their has been no leadership from the admittedly of no legal consequence, National Association of Boards of Pharmacy, although the head spoke out recently on the ABC

Evening News. I am hoping he will continue to do so, and lead the committee to make decisions, which are in the best interest of the US public, not to just to keep 3000 unnecessary pharmacies in existence.

EXHIBIT 1. (Perrin)

TRADE SECRET
PROFESSIONAL COMPOUNDING
CENTERS OF AMERICA, INC.

Time-Release Capsules

SUGGESTED FORMULA FOR TIME-RELEASE CAPSULES
#1 Capsules

Methocel (E4M) (This will occupy 40% of the volume of a #1 capsule.	100	mgs.
Active Ingredient (Up to 60% of the volume of a capsule may be occupied by the active ingredient)	...	...
Lactose or Corn Starch (If a filler is needed to complete the bulk of the capsule.)	...	...

SUGGESTED COMPOUNDING PROCEDURE

1. Weigh a medium packed #1 capsule full of the active ingredient. (weigh against a blank capsule)

2. Express as a percentage, the ratio of the desired amount of the active ingredient to the weight obtained in #1 above.
   Example: a medium packed #1 capsule contains 200 mgs. Progesterone. 100 mgs is the desired amount of active ingredient. 100 mgs/200mgs = 50%.

3. Add the percentage obtained in #2 above to the 40% of volume occupied by the Methocel, and subtract this total from 100% to find the amount of filler needed.
   Example: 50% (Progesterone) plus 40% (Methocel) = 90%. 100% - 90% = 10% filler needed. A #1 medium packed capsule contains approximately 400 mgs. Lactose. 10% of 400 mgs = 40 mgs.

4. The finished capsule using the examples above would have the following components.

   100 mgs Methocel = 40% volume of capsule
   100 mgs Progestrone = 50% volume of capsule
   40 mgs. Lactose = 10% volume of capssule
   240 mgs. = total weight of capsule