



MEMORANDUM

DATE: April 26, 2001

TO: Claudia Okeke, Ph.D.
Senior Scientific Associate
General Policies Requirements, Nomenclature, and Labeling Division
United States Pharmacopeia

FROM: Todd Siegel

SUBJECT: Beyond-Use Dating Guidelines

Please review this document and suggest any changes that you think may be appropriate. The current intention is to document our understanding of the situation and to educate our sales force, customer service staff and customers.

January 4, 2001

A meeting was held in Washington D.C. to discuss the recent change to the beyond-use date for oral solids repackaged in medication containers. Present were:

Todd Siegel, President, MTS Packaging Systems, Inc.
Michael Stevenson, Chief Operating Officer, MTS Packaging Systems, Inc.
Peter Gilbert, Vice President, Sales and Marketing, MTS Packaging Systems, Inc.
Kathy Jones, Director of Regulatory Affairs, NCS Vanguard, Inc. (consultant to MTS)

Members of the American Society of Consultant Pharmacists Legal Affairs Department, led by

Mary Jo Carden, R.Ph., Assistant Director of Government Affairs
Gary Riddle, Government Affairs Associate
Tom Clark, R.Ph., MHS, Director of Professional Affairs

Claudia C. Okeke, Ph.D., Senior Scientific Associate
General Policies Requirements, Nomenclature, and Labeling Division
United States Pharmacopeia (Dr. Okeke is the staff liaison to the USP Packaging, Storage and Distribution Subcommittee)

Background

The United States Pharmacopeia (“USP”), in part in response to requests from institutional pharmacies servicing long-term care facilities (“consultant pharmacists”), took under consideration a request for extended beyond-use dating for medications packaged into unit dose containers (primarily blister packs or punch cards). Consultant pharmacists have long felt that beyond-use dating for blister packs cards should be at least equivalent to the dating of vials and sought to have the USP review their guidelines to recommend a twelve-month beyond-use dating period for prescription medication repackaged and dispensed in unit dose blister packages. The previous beyond-use date was six months or 25% of the remaining manufacturer’s expiration date, whichever was less. The USP determined, from certain data, that polyvinyl chloride (“PVC”) does not provide adequate protection. The USP committee decided to approve a beyond-use date of one year when plastics having moisture barrier properties better than PVC were used. Three of the most popular high-barrier plastics in use today are a saran coated or laminated PVC (“PVDC”), an Aclar®* laminated PVC (Aclar), and polypropylene. The new USP regulation (see attached) allows beyond-use dating of one year when the dispensing pharmacy repackages into a unit dose container formed out of material “better than PVC”.

When the proposed guidelines were originally published in the *Pharmacopeial Forum*, there was little response or opposition from the industry. Most consultant pharmacists were either unaware of the publication or unclear as to its implication. It was generally perceived that the beyond-use date of the current PVC packages being used would be extended to twelve months. Having little or no opposition, the proposed policy was then adopted by the USP. The new policy raises many issues and concerns as outlined and discussed below.

- The USP is advocating that, in absence of stability dating, PVC should not be used for the repackaging of medications. Pharmacies are financially inhibited from performing stability studies and have no access to stability methodology. The policy states as follows: “*The plastic material used in repackaging must afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation.*” This statement is taken in context with the beyond-use dating of one year. The USP says they are silent on the use of PVC for pharmacies that wish to continue using this material.

The second portion of this statement, “.....*which does not provide adequate protection against moisture permeation*”, is also problematic. It is estimated that over 60% of pharmaceuticals packaged in the US are packaged in PVC. Thousands of drugs have undergone stability studies and have been able to justify expiration dates up to 2-3 years. While it is true that there are moisture sensitive drugs that should be packaged in high barrier plastics, they are not in the majority. Drug manufacturers and repackagers have seen an increase in use of moisture barrier plastics for the packaging of drug products into blisters due to the moisture sensitive nature of new drugs including many time-released formulations being introduced. Additionally, in order for drug companies to get product to market, they will perform an accelerated stability study, which subjects the blister package to high amounts of moisture and heat over a short duration of time, approximately 90 days. If the product passes the test, then a beyond-use date of 2 years is permitted and immediate market entry is achieved. Data from these rigorous test conditions and PVC MVTR values have been utilized by USP in coming to their conclusion relative to the moisture protection of PVC. However, this methodology is a conservative measure to assure that products entering the market will meet appropriate standards if manufacturers want to achieve

*ACLAR® is a registered trademark of Allied Signal Inc.

dating for quick market entry. Applying this data to justify a beyond-use date is inappropriate because a significant portion of products failing accelerated testing will pass shelf-life studies in a lower barrier film. Consultant pharmacists package products in room temperature conditions, transport product in temperature controlled vehicles and store products in room temperature nursing home facilities; therefore, never subjecting the package to the extreme conditions that may occur in a drug manufacturer's or a repackager's distribution process. Thus, using an accelerated stability test to determine the appropriateness of the use of PVC in the LTC industry is not representative of the conditions to which the containers are exposed.

- The use of barrier plastics creates production problems for both the converter of the blisters as well as the consultant pharmacist. (As used here, a converter, such as MTS, purchases plastic in roll form and, using wide-web thermoformers, produces blisters for later use at a pharmacy packaging operation.)

For converters, the forming of the high barrier materials is very difficult causing a productivity loss of approximately 50% and an increase in waste of approximately 10%. PVDC and Aclar are very soft materials and melt at low temperatures. With the types of thermoformers used by converters that pre-form blisters for later use in pharmacy practice settings, it is difficult to control the temperatures required in the blister forming process. In addition, these plastics are very tacky and create a problem releasing from the blister molds. As a result, the equipment must be slowed considerably. Polypropylene is virtually impossible to form in this process due to the specific characteristics of that material.

Converters are able to purchase PVC with a silicone coating. This reduces most of the tackiness and allows the PVC to run at higher speeds with less waste. In addition, the finished product is easier to separate (de-nest) at the pharmacy. Technicians and pharmacists separate thousands of blisters each day during the repackaging process. The manufacturers of plastic, such as Klockner Pentaplast, that produce PVDC and Aclar are prohibited from using silicone in those facilities since their primary customers, drug manufacturers and drug repackagers, do not need a silicone coating, and silicone was never included in their NDA or ANDA applications. As a result, plastic manufacturers never included silicone in their drug master files and are prohibited from having the material in facilities producing those materials. These plastic materials formed without silicone coatings are extremely difficult to de-nest and renders automated pharmacy packaging machines virtually useless.

Another operational issue pharmacies will face when using these materials is their poor sealing characteristics. Drug manufacturers and repackagers utilize industrial equipment with hydraulic cylinders that apply tremendous pressures in the sealing process. In addition, they are typically sealing foil to plastic and do not have the cardboard associated with punch cards. The cardboard creates an insulation or heat sync, which makes it more difficult to get enough heat to the foil so it will bond with the plastic material.

- The costs for using high barrier plastics are substantial. MTS estimates that approximately 221 million blisters are used by consultant pharmacists serving nursing homes, correctional and assisted living facilities. Additional costs to the industry in material alone for PVDC would be approximately \$11 million annually. In addition, converters would incur additional labor costs to produce the product, which would cost the industry an estimated \$3.3 million annually. MTS believes that pharmacies will incur pharmacy technician labor costs due to the problems associated with separating blisters formed with high barrier materials. Estimating this cost at approximately \$.03 per blister, would yield an additional cost of \$6.6 million annually. Making an assumption for additional profit margin charged by converters of 30% would yield an

additional \$4 million of cost. The total increase cost for PVDC is estimated to cost pharmacies servicing this industry approximately \$25 million annually or approximately \$.11 per blister.

The financial impact of using Aclar is even more significant. The increase in material cost alone is approximately \$19.8 million. Manufacturing labor and pharmacy technician labor are the same as PVDC at \$3.3 million and \$6.6 million respectively. Additional profit margin charged by converters is estimated at \$7 million. Based on these estimates, it would cost the industry approximately \$37 million annually or an additional \$.17 per blister.

Summary

In its meeting with the USP, MTS and ASCP reviewed these issues with Dr. Claudia Okeke, who is the USP liaison to the “**Packaging, Storage, and Distribution Sub-Committee**”. Dr. Okeke acknowledged that it was unfortunate these issues were not presented to the USP while the policy was noticed in the *Pharmacopeial Forum* during its “in-process revision” and has agreed to present the information contained in this memo to Dr. Thomas Medwick, the PSD Subcommittee Chairman. The subcommittee is due to reconvene in May, and it is anticipated that this topic will be reviewed. In addition, MTS has provided comments on the new policy and has recommended that the policy be revised to include a provision for the use of PVC under the previous standard of six months or 25% of the remaining manufacturer’s expiration date, whichever is less. We do not believe it is productive to pursue the USP for one-year dating using PVC material unless there is stability data to support this position. It was the pursuit of a one-year beyond-use date that brought about the current policy, and the subcommittee is not in favor of the use of PVC.

Until this situation is resolved, we do not recommend that pharmacies use one-year dating on their current packages. (Pharmacies should contact their State Boards of Pharmacy for guidance.) Additional courses of action would include educating State Boards of Pharmacy on this issue and having State Boards of Pharmacy, in conjunction with ASCP and its members, contact the USP to voice their concerns.

TS:dld