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BFGOODRICH
GEON VINYL DIVISION

INTER-ORGANIZATION CORRESPONDENCE
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To: Dr. Bob Hinderer
OTM - 3

Date: March 6, 1992

From: Chris Andersen

RELIANCE PETROCHEMICALS REBUTTAL

TOXICITY OF PVC USE FOR BLOOD BAGS

Reliance Petrochemicals Limited is our most recent operating licensee. The PVC portion of their 150,000 MTA VCM and PVC plant north of Bombay was successfully commissioned in December 1991. The VCM plant is currently being commissioned. The suspension PVC technology licensed by us is our current large poly technology and they are licensed for the full range of recipes including the low IV bottle resin (K-57 or 110X357).

Attached is a letter from their Product Application and Research Centre regarding several publications released in India which claim toxicity issues regarding the use of PVC in medical areas. I would appreciate your comment and if there are any literature or media releases which we could provide for their use in responding to the issues.

Thanks,

Chris Andersen

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P.V.C. FACTS - 1

D.E.H.P. (Di-2-ethylhexylphthalate ester)

For over 30 years the only collapsible non-venting intravenous containers commercially available were those manufactured from Polyvinyl Chloride. To provide the desirable physical characteristics, particularly clarity and flexibility, PVC contains significant quantities of plasticizers: some finished products may contain upto 40% of these plasticizers. Presently one commonly used group of plasticizer is phthalic acid esters, of which DEHP is the most widely used. Evidence has been accumulating to indicate that small quantities of plasticizers have been leaching from such materials into blood stored in PVC bags and into other I.V. solutions (1).

There have been reports earlier, that PVC containers have the tendency to release plasticizers as well as additives into the I.V. solution. But concern for possible health consequences from leaching of these plasticizers was not carried out until 1970 when Jaeger and Rubin (2) found conclusively the presence of DEHP (Di-2-ethylhexyl-pthalate ester) in tissues and organs of 2 deceased patients who had received blood transfusion from a PVC container plasticized with DEHP.

It has been found that PVC leached DEHP, a toxic substance and the toxicity increased as the percentage of additives increased (3).

Due to the increased concern and extensive debate on the toxic effects of plasticizers like pthalate ester present in PVC, many studies have been dedicated to this particular subject.

In 1972, Singh, Lawrence and Autian (1) published results which showed that phthalate ester plasticizers induced foetal malformations at high dose levels. The authors have commented that the possible cumulative nature of the effect of the plasticizer in the body should be considered and have supported the findings of Jaeger and Rubin (1) that the rat liver did not hydrolyse DEHP but tended to sequester and accumulate it.

Hillman, Goodman and Sherman in 1975 (4) demonstrated that the accumulation of DEHP in critically ill infants was high. DEHP was found, in the heart tissue of patients from the study group, having concentrations 9 times higher than those in the control group. It has been shown that due to the immature microsomal enzyme systems in newborns,they have difficulty in metabolising DEHP.

Autian (5) 1973, concluded that even though it is unlikely that pregnant women will be exposed to sufficiently high dose levels of pthalate ester to produce embryotoxic effects and birth defects, caution should prevail and expectant mothers should be afforded the maximum protection against these esters.

Furthermore, in PVC pouches, DEHP has been shown to be the causative factor for high particulate matter content. This is due to the liquid particles of DEHP which, in the resting position, adhere to the wall of the container, but on agitation are dispersed into the solutions.

The possibilities of interactions of drugs with the leached additives and induction of more extensive leaching by other drugs or solvents should be considered by ;the clinician. It has been shown that the plasticizer DEHP was a major leached chemical (3).

References:

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(2) Jaeger R.J., Rubin R.J. - Magration of Pthalate Ester Plasticizer from PVC Blood Bags into Stored Human Tissues. New Engd. Jou. of Med. Nov. 30, 1972 1111-1118.

(3) Moorhatch P. & Chiou W.L. - Interactions between Drugs and Plastic Intravenous Fluid Bags. American Jour. of Hosp. Pharm. 31, Feb. (1974) 149-152.

(4) Hillman L.S., Goodman S.L., Sherman W.R., - Identification and Measurement of Plasticizer in Neonatal Tissues after Umbilical Catheters and Blood Products, New Eud. Jr. of Med. 292 (1975) 382-386.

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P.V.C. FACTS - 2

PARTICULATE MATTER

The presence of particulate matter in parenteral solutions has been a problem since the advent of this route of administration. However, only recently these particles have been shown clinically to be injurious to humans (1).

Particulate matter has been defined as "The mobile, undissolved substances, unintentionally present in parenteral solutions".

Interest in particulates was first stimulated way back in 1963 by Garvan and Gunner. Further work was done by Gross of the F.D.A. of United States who stated that "It becomes evident, that particulate matter in I.V. solutions can be harmful (1).

Particulate matter can cause harmful effects such as pulmonary microemboli, thrombi or granulomas in patients (2). Particulate matter is the causative factor in 70% of the patients developing infusion phebits (3).

The highest amount of particulate matter is in P.V.C. pouches; about 3 to 4 times more that in glass or polyethylene.

A major cause of concern regarding the use of P.V.C. I.V. pouches is the possible diffusion of toxic stabilizers and plasticizers from P.V.C. into the I.V. solution P.V.C. pouches contain a host of various plasticizers, stabilizers and catalysts. One such plasticizer used is di-2-ethylhexyl pthalate ester DEHP also known as dioctyl pthalate (4).

A subsequent study by Whitlow et al (4) showed that the main causative factor for high particulate matter content in P.V.C. pouches was DEHP. The study was done by subjecting P.V.C. pouches to gyrorotatory agitation, to simulate conditions of truck moving on bumpy road. The P.V.C. pouches had as high as 20,000 particles/ml of size varying between 3 to 5 microns. This phenomenon was also identified due to the presence of DEHP in P.V.C. pouches.

The high particulate matter content in P.V.C. pouches may be related to the manufacturing process also since the bags are manufactured separately, apart from the filling stage. Leaching of plasticizer from the polymer may be another source of contamination (5).

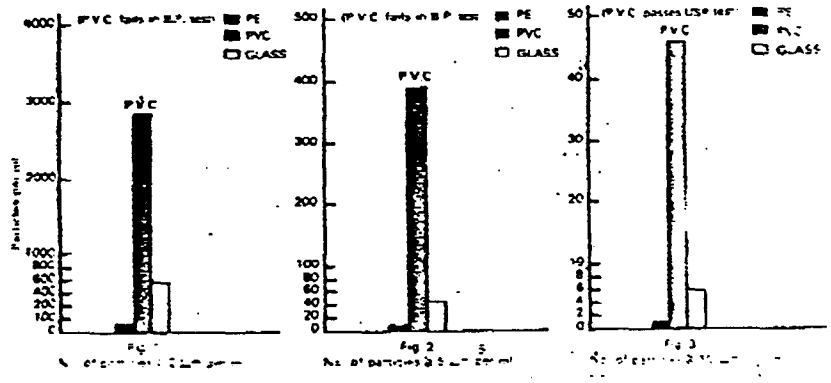
A study was conducted in 1987, comparing the particulate matter content (Figs. 1,2, & 3) present in P.V.C. pouches with glass and polyethylene containers, it was found that P.V.C. pouches generate maximum amount of particulates per ml. (5).

The findings of the above mentioned study is summarised below alongwith the Pharmacopoeial limits of British & U.S. Pharmacopoeia.

4

Type of container	No. of particles per ml.		
	> 2 Micron	> 5 Micron	> 10 Micron
P.V.C. Pouches	2800	390	46
Glass container	550	42	7
Polyethylene container	50	6	1
Pharmacopoeial limit	1000 (B.P.)	100 (B.P.)	50 (U.S.P.)

It has been shown that P.V.C. pouches containing infusion fluids contain additives. The increase in particulate matter is due to the high additive content in P.V.C. pouches (6).



In conclusion it can be mentioned that P.V.C. pouches tend to generate maximum number of particulate matter, much greater than the permissible limits given in the various pharmacopoeias.

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(1) Neil M., Turco S. Sivelly, E-A Study of Particulate Matter in I.V. Infusion Fluids - (American Jour. of Hosp. Pharm. Vol. 27 Oct. 1970 823.
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(5) Uotila, J. - Some Considerations on Particulate Matter Contamination and Proper Material Selection During the Development of Parenterals (Pharma. Industry 49) Sept. 1987 968-971.
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P.V.C. FACTS -4

MOISTURE VAPOUR TRANSMISSION RATE (M.V.T.R.)

PVC pouch looses 16% of its water content at 37°C over a period of 36 months, much before its expiry period. This increases the concentration of the drug present, by 16% during its shelf-life.

Moisture Vapour Transmission Rate (M.V.T.R.) can be defined as the rate at which water vapour will permeate a film or membrane at 100°F and 100% Relative Humidity during a 24 hour period.

During the process of water vapour permeation the following process takes place:

- From the high vapour side (ie. from inside the pouch) water dissolves into the barrier film.
- Water diffuses through the barrier film, at a rate proportional to the concentration gradient of water, through the barrier thickness.
- Water evaporates from the barrier surface into the low vapour (ie. outside the pouch) pressure side of the barrier (1).

Due to the process permeability, water vapour which diffuses out of the barrier is lost into the atmosphere, thus reducing the total water content inside the pouch. This causes an increase in the concentration of the drug present in the solution.

The permeation rate of PVC has been proved to be the highest amongst all plastics. In addition to PVC's high permeability to water vapour, it is also highly permeable to oxygen and carbon dioxide.

Stability studies conducted on PVC pouches show a high water transmission rate, Weighing solutions in PVC pouches, before and after storage, in simulated conditions, provide information about loss of content due to moisture vapour transmission (2). Another test which conclusively proves vapour loss is an increase in assay values of the ingredients present in the solution (2).

A study conducted on PVC pouches, containing I.V. solutions, showed that it lost

* 1.6% to 4% of its nominal value when stored at 25°C at 33% to 75% relative humidity after a period of 12 months.

Although this loss would not appear very significant, the increase in concentration changes of the drug present, resulted in a hypertonic solution. This study concludes that the PVC pouch is not a truly closed system and there exists a potential for gaseous entry into the system (3).

In India, where the average temperature is 37°C, the total weight loss and increase is solute concentration in PVC pouches was

* 16% over a period of 36 months. This would lead to the concentration of the drug in the pouch, to increase by 16% much before its expiry period.

Thus in a country, where air-conditioning is not available, this would reduce the shelf-life to less than 1 year. The various pharmacopoeias allow a variation of the concentration of the drug present at ±5% during its shelf life.

This study clearly demonstrates the unviability of PVC pouches in a country like ours, where the ambient temperature is always high.

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