U.S. Department
of Transportation

**Research and
Special Programs
Administration**

400 Seventh Street, S W
Washington, D C. 20590

NOV 19 1998

Mr. James R. Hendricks
Manager, Dangerous Goods Compliance
GlaxoWellcome, Inc.
P.O. Box 13398
Research Triangle Park, NC 27709-3398

Ref. No. 98-0303

Dear Mr. Hendricks:

This is in response to your letter in which you request clarification concerning the definition of "biological product," as used in the Hazardous Materials Regulations (HMR; 49 CFR parts 171-180) and in the regulations of the Food and Drug Administration (FDA) of the Department of Health and Human Services (21 CFR part 312 and parts 600 to 680). I apologize for the delay in responding to your inquiry.

Your letter is quoted, in part, as follows:

> An infectious material which meets the FDA definition of "biological product," as defined in 21 CFR Part 312 or 21 CFR Parts 600-680 may be shipped in any additional packaging; essentially non-regulated. Our question is whether an infectious material which does not meet the FDA definition of "biological product" while outside a "medical device," automatically becomes a "biological product" when placed into a "medical device?"
>
> Our confusion results from the fact a packaging manufacturer currently offers a package that has been registered with the FDA as a "medical device;" with the implication that any biological material inside a registered medical device (including infectious materials) may be treated as a biological product.
>
> Our understanding of the FDA definition of "biological product" does not include mention of "medical devices." Furthermore, we do not believe the two terms are inter-related. Although our question may be more appropriately directed to the FDA, we would appreciate RSPA's response/comments to the following question: Does an infectious material that is not a "biological product" outside a FDA-approved medical device become a "biological product" when placed inside the medical device?

We agree that it does not appear that a medical device meets the FDA definition of "biological product" in 21 CFR 600.3(h). However, you are correct that it would be more appropriate to address your question concerning this definition to the FDA.

Under the HMR, a material which meets the definition of "biological product" in 49 CFR 173.134(a)(3) is excepted from regulation. With regard to FDA regulations, the HMR definition applies only to materials prepared and manufactured in accordance with 21 CFR part 312 (Investigational new drug application) and 21 CFR 600 to 680 (Biologics). If a material is not prepared and manufactured in accordance with these regulations, it is not a biological product under the HMR. An infectious material that is not a biological product does not become a biological product by the act of placing it in an FDA-registered medical device and, unless otherwise excepted, is fully subject to the HMR.

For your information, we have been in contact with the packaging manufacturer and they have agreed to discontinue making claims that might imply that an infectious substance becomes a biological product when shipped in their packaging.

I trust this satisfies your inquiry. If we can be of further assistance, please contact us.

Sincerely,

Edward T. Mazzullo

Edward T. Mazzullo
Director, Office of Hazardous
Materials Standards

GlaxoWellcome

Manager, Dangerous Goods Compliance

October 20, 1997

U.S. Department of Transportation
Director-Office of Hazardous Materials Standards; DHM-10
400 Seventh Street, S.W.
Washington, Dc 20590-0001

Subject: Request for Clarification

The purpose of this correspondence is to request clarification regarding DOT and FDA criteria for classification, packaging and transportation of infectious materials, including biological products.

An infectious material which meets the FDA definition of "biological product," as defined in 21 CFR Part 312 or 21 CFR Parts 600-680 may be shipped in any additional packaging; essentially non-regulated. Our question is whether an infectious material which does not meet the FDA definition of "biological product" while outside a "medical device," automatically becomes a "biological product" when placed into a "medical device?"

Our confusion results from the fact a packaging manufacturer currently offers a package that has been registered with the FDA as a "medical device;" with the implication that any biological material inside a registered medical device (including infectious materials) may be treated as a biological product.

Our understanding of the FDA definition of "biological product" does not include mention of "medical devices." Furthermore, we do not believe the two terms are inter-related. Although our question may be more appropriately directed to the FDA, we would appreciate RSPA's response/comments to the following question: Does an infectious material that is not a "biological product" outside a FDA-approved medical device become a "biological product" when placed inside the medical device?

Perhaps a specific example may assist in your response: Could a blood sample containing the organism *Vibrio vulnificus*, which has caused septic shock syndrome in the person from which the sample was drawn, be shipped as a biological product, if shipped in a FDA-approved medical device? *Vibrio vulnificus* is not on the 42 CFR 72.3 list of certain etiologic agents, nor does the blood sample meet the FDA definition of "biological product" prior to preparation for shipment.

Thank you for your consideration. We anxiously await your response.

Regards,

James R. Hendricks

Glaxo Wellcome Inc.

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ISSUE PAPER
Response to 10/20/97 Letter from James R. Hendricks
of Glaxo Wellcome, Inc. (GWI)
RE: Can an infectious substance that is not a biological product become a biological product solely because it is placed in an FDA-approved medical device?

GWI Issues:

* GWI says Pro-Tech-Tube (PTT) presented them with literature that makes it appear to GWI that an infectious substance that is not a biological product, such as a diagnostic specimen, becomes a biological product if it is placed in an FDA-approved medical device. PTT also presented GWI with their packaging, which GWI presented to RSPA. This packaging was stamped **"UN1H2V/X.2/S/92/USA/M4578/DOT-E10148/ RESTRICTED: BODYFLUIDS AND EXCRETIONS ONLY."** On the bottom of the packaging is the wording "Supreme Plastics Inc. White Oak, Texas"

* The written materials GWI submitted are from Andwin Scientific, a Division of the Andwin Corporation, 6636 Variel Avenue, Canoga Park, CA 91303, (818)999-2828, FAX 818(999-0111). They contain promotional literature on how to use the Safetex clinical shipper, which is really PTT's device. The materials also include a letter and instructions from PTT. In these materials are the phrases:

> "You really can ship infectious substances, in limited quantities (50 ml or less), in the Safetex ™ Clinical Shipper as biological products."
>
> "...you are allowed to ship an infectious substance as a biological product and be exempt from DOT hazmat regulations."
>
> "Shipped quantities of medical specimen, limited to the Directions for Use, are "*biological products*"as defined by FDA, and are to be treated just as you would treat the transportation of a potentially dangerous attenuated live virus vaccines."
>
> "The FDA definition for biological product means any virus . . . Paragraph (1) states a virus is interpreted to be a product containing the minute living cause of an infectious disease... The manufacturer's claim to FDA states: microorganisms placed in the *shipper* are FDA regulated biological products."
>
> "Biological products are products made from living organisms. They consist of substances that can be part of an aid to diagnosis, mitigation, treatment or prevention of diseases in man."

[RSPA Note: The "directions for use" do not define biological product but forbid the packaging to contain volumes exceeding 50 ml or 50 g; Biosafety level 4 materials "which pose a high individual risk of aerosol-transmitted laboratory infections and life threatening disease" and any material with a close or identical antigenic relationship to these materials; agents found in 42 CFR Part 72 as select agents, Appendix A to Part 172, or in NIH publications Biosafety in Microbiological and Biomedical Laboratories or "Actions Under the Guidelines."]

* GWI recognizes it needs FDA to define biological product, but has approached RSPA asking its staff to make this call. They may be encountering difficulty obtaining this information from FDA. Historically, FDA has been slow to respond to RSPA on definition and packaging issues involving biological products. The response RSPA formally submitted to FDA's Dr. Katherine Nzoom, Director of the Center for

E. Edmonson ~~10/5/98~~ 11/18/97 E.E.

Biologics and Research several years ago asking for clarification on how the agency defines biological products and ensures packaging integrity for these materials in transportation was never answered.

* GWI doesn't believe PTT's claims that its packaging meets UN performance standards. GWI is reluctant to use PTT's packagings without assurances from DOT that it is acceptable. GWI reported in conversations with RSPA staff that it is concerned about any liability it may experience from using the packagings, and stated other shippers of Division 6.2 materials are also reluctant to use PTT's packagings without further assurances from DOT.

PTT's Issues:

* On October 30, 1997, PTT sent RSPA several of their packagings stamped "**UN 1HH2U Class 6.2 96/M4395 USA**," directions for using the packaging, and the FDA letter approving the packaging as a medical device (which includes a description of the product and the results of the penetration test). PTT submitted a copy of their test results, patent information and diagram to RSPA on August 20, 1997.

* In an 11/97 conversation with Ms. Edmonson, Mr. Warder said he once spoke with Dr. Richard Knudsen, Chief, Biological Safety, Centers for Disease Control and Prevention, about the PTT packaging and Dr. Knudsen objected to its design. Mr. Warder said Dr. Knudsen informed him that the design of packages for diagnostic specimens must meet CDC requirements. Ms. Edmonson told Mr. Warder Dr. Knudsen's statement was correct.

* On 11/17/97, Mr. Warder stated in a telephone conversation with Ms. Edmonson that the packagings PTT sent RSPA on October 30, 1997, were the result of a run of incorrectly marked packagings. He provided a facsimile of the markings currently in use, which describe the packaging as a "**UN 6HH1U/class 6.2 (50 ml)/S/97/USA/ M4578**," which meets ICAO marking requirements for a Division 6.2 packaging. The facsimile included a second marking "**UN 6HH1U/50ml/97/USA/M4578**", which appears to be missing the notation for packing group.

FDA Issue:

* Mr. Steve Falter, Director, Regulations and Policy Staff, Center for Biologics Evaluation and Research, HFM-17, Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, (301)827-6210, FAX (301)443-3874, in a 11/18/97 conversation with Eileen Edmonson stated that an FDA-approved medical device is approved to transport biological products for humans. He said the device does not determine whether a material meets the definition of a biological product. He said a biological product is defined in Section 351 of the Public Health Service Act and, in general, is a material developed for the prevention and treatment of injuries of man; that it must be licensed in interstate commerce; and that it must be safe, pure and potent for its intended use. He said the statements in the Andwin literature are incorrect and requested copies of them to present to FDA's enforcement office. Ms. Edmonson supplied him with these materials by facsimile on 11/18/97.

RSPA Issues:

* RSPA denied PTT the reissuance of the exemption DOT-E 10148 because it was for biological products and diagnostic specimens, products that are not currently regulated under the HMR.

* GWI doesn't believe PTT's claims that its packaging meets UN performance standards. GWI is reluctant to use PTT's packagings without assurances from DOT that it is acceptable. We can respond to this issue, PTT has supplied us with their test data, directions for use, and an example of the packaging.

* Currently, there are no package specification marking requirements for Division 6.2 packagings in the United States. However, there are package marking requirements under the International Civil Aviation Organizations (ICAO) Technical Instructions. In a 4/9/97 conversation with Mr. Bill Warder, President of PTT, Ms. Eileen Edmonson informed him there was no UN specification 1HH2 and the manufacturer's marking "M4395" represented the Cooper Drum, Co., in South El Monte, CA. Ms. Edmonson informed Mr. Warder the correct packaging specification reference was either 1H2 (removable head plastic drum) or 6HH2, that she incorrectly informed him was a removable head composite plastic drum. Mr. Warder stated the correct reference was 6HH1 for a plastic receptacle within a protective plastic drum. Also, Ms. Edmonson informed Mr. Warder that the correct manufacturer's marking for PTT was "M4578." The symbol "U" represents special packaging under Section 6.4 of ICAO's Technical Instructions. The "U" symbolizes that the inner receptacles of any type may be assembled within an intermediate (secondary) packaging and transported without testing in the outer packaging under certain conditions.

Questions:

* Does DOT have the authority to say the definition of a biological product is determined by the type of packaging used? Although, historically, we have excepted hazardous materials from regulation based on packaging safety, the answer is no.

* Does the Pro-Tech-Tube packaging meet the performance criteria in § 178.609 (for infectious substances)? In § 178.522 (for composite packagings with inner plastic receptacles)? Materials and packagings submitted to RSPA by PTT were forwarded to DHM-20 on 11/18/97 for their review.

* Does it matter that the packaging meet the criteria in § 178.609 to be an acceptable packaging for biological products since we currently do not regulate biological products? No.

* What specifically is the FDA's definition for biological product; is it tied to its use in a medical device? On 11/13/97, Ms. Ann Wion, Deputy Chief Counsel for Program Review (301-827-1143) referred me to Mr. Steve Falter, FDA Center for Biologics and Research (301-827-6210, ext. 5) to obtain an answer to this question. Mr. Falter responded on 11/18/97. See FDA Issue.

Recommendations for response to GWI:

* Clarify that the biological products definition is solely FDA's to determine.

* Provide our comments on the packaging and its test results.