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METHOD OF PACKAGING VIRAL ANTISERA AND OTHER RESEARCH DIAGNOSTIC REAGENTS

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25 Claims

ABSTRACT OF THE DISCLOSURE

Method of providing a plurality of vials or packages of viral antisera or reagent from a common lot, each of which has a uniform, homogeneous equal content and moisture content and a long shelf life, in lasting compliance with and adherence to the required standard and specifications, by treating the batch or lot of viral antiserum or reagent to be packaged or vialled in bulk by freeze drying (lyophilize) the same, if necessary, pulverizing or grinding the dried serum to a uniform size and consistency, vacuum drying the bulk lot of powdered serum, with stirring or agitation, if desired, to obtain a lot of serum having a uniform, homogeneous, moisture content, powder filling the separate vials or packages of the lot under sterile, moisture free conditions to a uniform fill and content, and sealing the separate vials or packages with a dry moisture free and proof seal.

This invention relates to a new and improved method and process for packaging or vialing moisture free viral antisera and other diagnostic reagents, vaccines, and the like; to a new and improved method and process for packaging or vialing a plurality of containers, of uniform, homogenous viral antisera and other diagnostic reagents, vaccines, and the like, from a single lot and, more particularly, to a new and improved method and process for packaging or vialing viral antisera for use as research reference reagents and the like.

It is customary to package viral antisera, and the like, in vials for distribution and use as standard reference reagents. Such vialled antisera is prepared to uniform standards in a plurality of vials or separate packages from a given lot, batch or bulk supply with the expectations that the antisera will remain up to standard in quantity, uniformity, quality and moisture content over extended periods of times or for a long shelf life so that subsequent researchers and users are assured of reference, or other diagnostic, reagents for use in research projects, and the like, which, in fact, are sterile and comply accurately with the standards established for the particular reference reagent as published and distributed to users of the reagent. One of the most important criteria which must be met upon original packaging of vialing of the antisera, or other reagent, and which must be maintained throughout the shelf life of the respective vials of antisera or reagent is moisture or, more appropriately, lack of moisture content.

Further, if the respective vials are to be true standards, in fact, the moisture content must be the same in each vial of a given lot and, if the reagents are to retain their standard characteristics throughout their anticipated shelf life, the moisture content of each vial must, in fact, be below the maximum allowed from the time of sealing to the time of use. Also, it is preferable that the vials of reagent not be reduced, during the drying process, to a moisture content below the maximum permitted by the standard or specifications and then permitted to increase to a higher moisture content, even though the latter, higher content be within the maximum allowed under the ap-

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plicable standard and specifications. The long accepted prior practice and custom in the art, for vialing viral antiserum is set forth, for example, in "General Specifications for Lyophilization and Packaging of Research Reagents," as revised Feb. 24, 1966, by the Research Reference Reagents Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Analyses and studies of previously packaged and vialled standard reference viral antisera have established that vials of viral antisera, which have been prepared by freeze drying and sealing under vacuum and accumulated in the expectation that they would and could function and, in fact, be standard reference reagents having a long shelf life such that the standard and specifications of the respective vials would exist and continue to exist over long periods of time, while under acceptable and accepted storage and shelf life conditions, frequently had a moisture content exceeding specifications or standard and that the individual vials varied considerably in dried sera content, apparently because of differences in original moisture content. And, this has been so even though the samples, which were tested during the original preparation of the vials, were within the prescribed standard and specifications.

The general object of this invention is, therefore, to provide a new and improved method and process for packaging or vialing viral antisera and other diagnostic reagents, vaccines, and the like, for use as standard reference reagents, and other purposes, wherein individual packages of a given lot are uniform in moisture, quantity and quality content.

Another object of this invention is to provide a new and improved method and process for packaging or vialing viral antisera, and the like, within the meaning of this invention, which ensures that the content and characteristics of each vial of each lot of antisera or reagent is the same or substantially the same and has a homogenous residual moisture content which is within and remains within the permissible specifications and standard throughout the "life" of the vial.

Still other objects of this invention include the provision of a new and improved method and process for packaging or vialing viral antisera, and the like, within the meaning of this invention, for use as standard reference reagents, and other appropriate purposes, which is efficient and effective; which ensures that the vials or packages of a predetermined lot have a full, properly moisture free content; which provides even, effective and proper drying of the entire lot to a common homogenous residual moisture content so that the reagent in one vial or package does not differ in a meaningful way in moisture content from that in the other vials or packages of the same lot; which provides an improved and proper drying procedure; which prevents the reintroduction of moisture into the contents of the respective vials or packages, after packaging is complete; which ensures a properly dried and sterile filling, to constant fill level, of each vial or package of a given lot; and, which provides vialled or packaged vial antisera or other reference reagents, and the like, which are the same for each lot, and which have a long shelf life and maintain their standard and specifications throughout such shelf life.

Still further objects of this invention include the provision of a new and improved method and process for packaging or vialing viral antisera standard reference reagents, and the like, within the meaning of this invention which is adapted for use with standard or substantially standard or easily modified apparatus; which is safe and foolproof in operation; which does not contaminate or otherwise adversely affect the reagent; and, which is useful for lots of reagent of a wide initial range of moisture characteristics and volume.

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A still further object of this invention is to provide a new and improved method and process for packaging or vialing viral antisera, and the like, within the meaning of this invention, obtaining one or more of the objects set forth above.

These and other objects and advantages of this invention will appear from the following description of preferred and modified forms thereof.

Briefly the process of this invention, in contrast with prior art and practice followed with respect to the packaging or vialing of viral antisera standard reference reagents, and the like, within the meaning of this invention, comprises providing a plurality of vials or packages of viral antisera or reagent from a common lot, each of which has a uniform, homogenous equal content and moisture content and a long shelf life, in lasting compliance with and adherence to the required standard and specifications, by treating the batch or lot of viral antiserum or reagent to be packaged or vialled in bulk, to freeze dry (lyophilize) the same; pulverizing or grinding the freeze dried serum to a uniform size and consistency; vacuum drying the bulk lot of powdered serum, with stirring or agitation, if desired, to obtain a lot of serum having a uniform, homogenous, moisture content; powder filling the separate vials or packages of the lot under sterile, moisture free conditions to a uniform fill and content; and sealing the separate vials or packages with a dry moisture free and proof seal.

In those instances where the moisture content of the lot or batch of serum or reagent is initially sufficiently low, the lot may be pulverized or ground before lyophilizing or, if the moisture content is sufficiently low, the lyophilizing step may be dispensed with, provided the objects and purposes of this invention are otherwise obtained.

The method and process of this invention while particularly adapted for use either with a starting serum, diagnostic reagent, vaccine, and the like which is a frozen (or unfrozen, for that matter) liquid or solution, or a solid of a unitary, monolithic or divided granular or larger nature, but, not suitable for packaging or vialing because, inter alia, of a moisture content exceeding specifications or standard.

The method and process of this invention while particularly adapted for packaging or vialing viral antisera standard reference reagents may have a wide range of applications in the preparation, from a single lot of a reagent, within the meaning of this invention, having excessive moisture content of a plurality of separate packages, vials, ampoules, or the like, each of which has a uniform content of reagent having an homogenous moisture content and a long shelf life, during which the moisture content remains stable and the reagent does not depart from the set and expected specifications and standard.

The invention is exemplified below by the detailing of a preferred form thereof particularly adapted for use in preparing vialled viral antisera for use as standard reference reagents and by pointing out modifications to the preferred form of this invention by which bacterial antisera, vaccines and other reagents, within the meaning of the invention, may also be provided as a plurality of vialled or packaged units containing uniform, homogenous moisture free contents from a single lot.

Viral antisera for standard reference reagents is generally provided as a frozen solution in a bulk package which is thawed or otherwise released from the package, in which it is shipped, and filtered, both under sterile conditions.

In accordance with the precepts of this invention the batch or lot of filtered viral antisera is freeze dried or lyophilized, to eliminate the water of solution and reduce the moisture content sufficiently to permit the carrying out and accomplishment of the other steps of the method and process of this invention. Lyophilizing is accomplished generally in a manner known to the art and specifically for viral antiserum may be accomplished as set

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forth in the Bulletin of the Parenteral Drug Associations, vol. 20, No. 2, March-April 1966, pp. 39-47.

After lyophilizing is completed, the bulk antiserum is ground or comminuted, under sterile conditions, into a fine homogenous powder, preferably of about 80 mesh.

The powdered antiserum is then vacuum dried, in sterile apparatus, over a suitable desiccant, preferably molecular sieve, until, upon testing, the moisture content of the bulk antiserum has been reduced to that required by the standard or specifications.

Drying of the antiserum in bulk and in powdered form to the desired standard and specifications provide a homogenous serum lot which is much more quickly and evenly dried and freed of its moisture content, because of the homogenous physical nature of the antiserum when in powdered form, and the large surface and of the powder vis-a-vis the total quantity of antiserum in the lot.

For viral antiserum, the vacuum chamber is preferably flushed with nitrogen before use. The viral antiserum lot is dried in vacuo at 25° C. for about thirty-six hours or until the moisture content at the corners and center (and at and below the surface) of the tray or bulk container of powdered antiserum being dried not only meets specifications but is the same within plus or minus 0.2%. Note, when the volume of powdered antiserum is such that a plurality of trays or containers of powdered antiserum are prepared for vacuum drying in a single drier, that the samples from all of the trays must assay within plus or minus 0.2% in order to ensure that the antiserum is homogenous in moisture content. Further, the contents of the separate trays are intermixed before filling of the separate vials or packages in accordance with the precepts of this invention, as explained below.

Also, if desired, the powdered antiserum may be stirred or agitated during vacuum drying to increase the drying rate and accelerate and ensure obtaining of homogenous conditions throughout the powder mass.

After vacuum drying, the antiserum of a given lot or batch is filled into a plurality of separate vials or packages. Pending filling, the dried antiserum may be stored, if desired, in sterile, dry stainless steel beakers in a sterile, anhydrous atmosphere in a desiccator over molecular sieve.

The antiserum of a given lot is filled, under sterile conditions, in a conventional, for example, preferably high speed, filling apparatus. Each vial, for example, is first thoroughly dried and then purged with sterile anhydrous nitrogen, or other suitable, inert gas immediately before filling. Further, the vials are blanketed with the same or a similar sterile, anhydrous inert gas until sealed and a positive pressure and protective atmosphere is maintained on and about the powder in the filling machine with the same or a similar sterile, anhydrous inert gas. Each vial is filled to the predetermined amount and, since the powder is homogenous and the antiserum reduced to prescribed moisture content according to a predetermined standard and specifications, before filling, the actual amount of antiserum in each standard reference vial will, in fact, be the same and the residual moisture content of each vial will be the same, upon filling, as each other vial in the same lot, because of the homogenous nature of the dried powdered bulk antiserum in the lot.

Immediately, within seconds, after filling, the vials of packages of antiserum are sealed under sterile, dry conditions with a sealing means which is absolutely dry and will not or cannot, as in past practice, be a means or source from which moisture is reintroduced into the vialled antiserum of a particular vial or package.

The use of caps, stoppers or closure members which are separately, thoroughly dried, instead of being dried simultaneously with the antiserum in the separate vials, as in the past standard practice with respect to such standard reference reagents, ensures that there is no resid-

ual moisture, which might otherwise, and frequently, apparently, did, remain entrapped within the cap, stopper, or closure member, when the antiserum content tests to the desired moisture level reenter the vial after packaging is completed to contaminate the antiserum. Thus, this invention precludes reintroduction of moisture into the antiserum after packaging or vialing is completed.

As noted above, when the original bulk reagent is sufficiently dry, and lyophilizing is still desired, the reagent may be powdered, or at least granulated, before lyophilizing, if desired under all the circumstances.

Modifications, changes and improvements to the preferred and modified forms of the invention herein particularly disclosed and described may occur to those skilled in the art who come to understand the principles and precepts thereof. Accordingly, the scope of the patent issued hereon should not be limited to the specific forms of the invention herein particularly illustrated, disclosed and described but only consistent with the advance by which the invention has promoted the art.

I claim:

1. A process for preparing a plurality of vials of dried, homogenous, sterile viral antiserum, for use as standard references, from a single lot of bulk antiserum including the steps, accomplished under sterile conditions, of comminuting the bulk antiserum, vacuum drying the comminuted viral antiserum in the presence of a desiccant sampling the comminuted viral antiserum during the drying step until the sampling indicates a uniform, homogenous moisture content throughout said lot of bulk comminuted viral antiserum as set by a predetermined standard and specifications, filling a plurality of separate, sterile, dry vials with a predetermined, standard amount of said viral antiserum from said lot in an anhydrous, inert atmosphere, and closing each said vial, immediately after filling, with a dry, moisture proof seal, while maintaining the contents of each said vial dry, sterile and uniform in accordance with said predetermined standard and specifications.

2. The process according to claim 1 in which said lot of bulk viral antiserum is vacuum dried in the presence of molecular sieve.

3. The process according to claim 1 in which said lot of viral antiserum is vacuum dried at about 25° C.

4. The process according to claim 1 in which said lot of bulk viral antiserum is vacuum dried in a plurality of separate containers in a single chamber.

5. The process according to claim 4 in which all samples of said dried lot of antiserum are tested for moisture content within said predetermined standard and specifications and within 0.2% of each other.

6. The process according to claim 1 in which all samples of said dried lot of antiserum are tested for moisture content within said predetermined standard and specifications and within 0.2% of each other.

7. The process according to claim 1 in which said lot of viral antiserum is stirred or agitated during vacuum drying.

8. The process according to claim 1 in which said lot of viral antiserum is lyophilized to a predetermined moisture content before vacuum drying.

9. The process according to claim 8 in which said lot of viral antiserum is comminuted before lyophilizing is completed.

10. The process according to claim 1 in which said closing is accomplished with a separate closure member which becomes a part of the completed vial.

11. The process according to claim 10 in which said closure member is separately dried and sterilized before application to said vial.

12. The process according to claim 11 in which said closure member is pilferproof.

13. A process for preparing a plurality of packages of a dried, homogenous, sterile reagent, for use as standard references, from a single lot of bulk reagent including

the steps, accomplished under sterile conditions of comminuting the bulk reagent, vacuum drying the comminuted reagent in the presence of a desiccant, filling a plurality of separate, sterile, dry packages with a predetermined, standard amount of said reagent from said lot in an anhydrous, inert atmosphere, and closing each package, immediately after filling, with a dry, moisture proof seal, while maintaining the contents of each said package, dry, sterile and uniform in accordance with said predetermined standard and specifications.

14. The process according to claim 13 in which said lot of bulk reagent is vacuum dried in the presence of molecular sieve.

15. The process according to claim 13 in which said lot of bulk reagent is vacuum dried in a plurality of separate containers in a single chamber.

16. The process according to claim 13 in which said lot of reagent is stirred or agitated during vacuum drying.

17. The process according to claim 13 in which said lot of reagent is lyophilized before vacuum drying.

18. The process according to claim 17 in which said lot of bulk reagent is comminuted before lyophilizing is completed.

19. The process according to claim 13 in which said closing is accomplished with a separate closure member which becomes a part of the completed package.

20. The process according to claim 19 in which said closure member is separately dried and sterilized before application to said package.

21. A process for preparing a plurality of vials of dried, homogenous, sterile viral antiserum standard reagent from a single lot of bulk viral antiserum including the steps, accomplished under sterile conditions, of lyophilizing the antiserum to a predetermined moisture content, comminuting the lyophilized viral antiserum, vacuum drying the comminuted reagent at 25° C. in the presence of a molecular sieve sampling the comminuted viral antiserum during the drying step until the sampling indicates a uniform, homogenous moisture content throughout said lot of bulk comminuted viral antiserum as set by a predetermined standard and specifications, filling a plurality of separate, sterile dry vials with a predetermined, standard amount of standard viral antiserum from said lot in an anhydrous, inert atmosphere, and closing each vial, immediately after filling, with a separately dried, sterile, moisture proof closure member, while maintaining the contents of each said package, dry, sterile and uniform in accordance with said predetermined standard and specifications.

22. The process according to claim 21 in which said lot of viral antiserum is stirred or agitated during vacuum drying.

23. The process according to claim 13 in which all samples of said dried lot of reagent are tested for moisture content within said predetermined standard and specifications and within 0.2% of each other.

24. The process according to claim 1 in which said viral antiserum is comminuted to about 80 mesh.

25. The process according to claim 21 in which all samples of said dried lot antiserum are tested for moisture content within said predetermined standard and specifications and within 0.2% of each other.

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