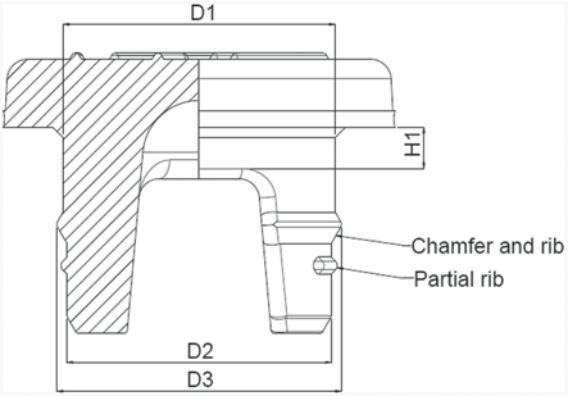

Fig. 4 A particular design of freeze-drying closure

dimensioning. Only a minimum number of dimensions are standardized. This is a consequence of so many lyophilization stopper geometries having been developed and being made available to the market over time. One feature that leads to diversity is the number of vent openings. In Fig. 4, there are two vent openings that are symmetrically located over the plug circumference ("2-leg-lyo-stopper"). Other designs have three vent openings ("3-leg lyo stopper"). A frequently encountered stopper type has only one, but then a larger vent opening ("igloo stopper"). All of these stoppers are illustrated in Fig. 2.

Splitting the vent area over multiple openings also has other consequences that become apparent at the time of lyo cake reconstitution and preparation of the injection into the patient. The single large vent opening of the igloo-type stopper on the left-hand side in Fig. 2 allows to follow the introduction of the needle through the stopper penetration area into the vial, at least if the turbidity of the reconstituted solution and the size[2] of the stopper both permit this. The needle is attached to a syringe in which the drug solution is collected before injection into the patient. With the igloo type of stopper it therefore is possible to visually follow how much of the vial drug solution is transferred into the syringe and eventually into the patient. There thus is a contribution of the stopper design to minimization of the residual volume of the vial. With a 2-leg stopper, this is already not easy anymore. With a 3-leg stopper, it is not possible at all anymore, since the cannula tip will always be hidden, if not by the crimp cap, then by the legs of the rubber stopper. Moreover, with this type of stopper, there is the additional disadvantage that when the stopper is in fully seated position, the legs are forced to come together. Thereby, capillaries are formed between the legs in which reconstituted drug solution is held up. Such 3-leg designs therefore increase the residual volume in the vial. A last disadvantage of 3-leg designs is that during packaging at the closure manufacturer or during transport to the user of the closures, the legs get entangled, resulting in "twin pairs" of stoppers that do not separate again and that disturb good machineability behavior on filling lines.

[2] It depends on the actual igloo design whether this is possible or not. With some designs it is, with others it is not.