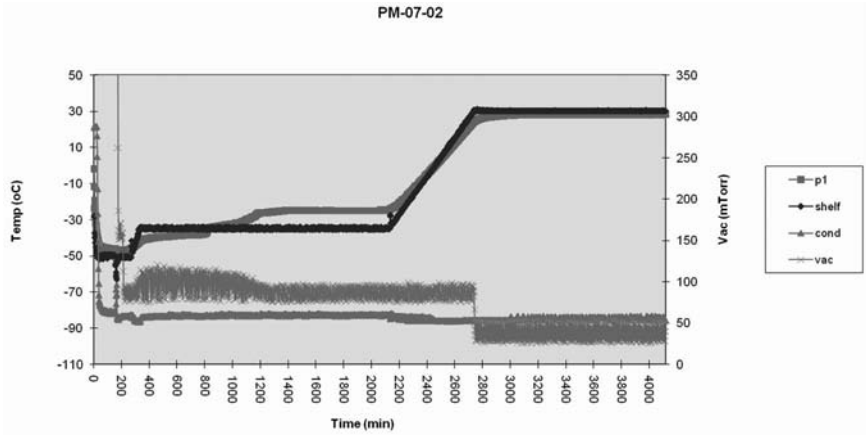

FIGURE 7 Typical lyophilization cycle developed at pilot scale showing product temperature probe inflection and drop in pressure as indicators of end of primary drying. *Source*: From Ref. 10.

by the processing team to detect and deal with any deviations or potential problems. Typical parameters measured are shelf temperature, product temperature, condenser temperature, condenser, and chamber vacuum; these are compared to the set points in the freeze-drying cycle used. All recordings are attached to the Product Record.

At the end of freeze-drying, the chamber is restored to atmospheric pressure with pure, dry nitrogen, and the ampoules/vials are fully stoppered by contracting the shelf stack and then removed. The ampoules/vials are then sealed or overcapped (see sect. "Sealing/Capping").

Further Desiccation

Further desiccation over phosphorus pentoxide following the freeze-drying was practiced at NIBSC for some reference materials until 2005 to ensure very low moisture contents. However, by optimizing freeze-drying cycles accordingly residual moisture levels of <1% wt/wt can typically be achieved without resorting to such additional processing. Indeed in comparative studies of labile biological activities (factor V and factor VIII activity in plasma), Hubbard et al. (11) showed that not only did the nondesiccated material have adequate stability similar to the further desiccated material but that stability was also dependent as much on appropriate formulation as ultralow moisture content. Addition of glycine and in particular glycine plus hepes buffer gave greater stability of the factor VIII activity at 20°C storage without further desiccation of the product than for the desiccated product (Table 2).

Sealing/Capping

Whereas manual sealing may be suitable for small numbers of ampoules [e.g., using a semiautomated machine from Adelphi Tubes Ltd., (Haywards Heath, W Sussex, U.K.)], to deliver the consistency and quality required for International Standards an automated flame sealer is required (Fig. 8).