the device used in our study (the Baxter Infusor) states that the flow rate increases by about 0.5% for every 1-in rise in head height and by about 2.3% (due to a reduction in solution viscosity) for every 1 °C rise in temperature.[1] Also, the flow rate depends on the type of solution used. For example, the flow rate for 0.9% sodium chloride injection is about 10% higher than that for 5% dextrose injection. For temperature control, we recommend taping the flow-restrictor housing to the skin. An internal study found that this is a very effective method for minimizing the effect of ambient temperature variation.

1. Baxter elastomeric pumps clinician guide. Ontario, Canada: Baxter Corporation; 2010.

Jong Wang, Ph.D., Engineering Specialist
Baxter Healthcare
17511 Armstrong Avenue
Irvine, CA 92614
jong_wang@baxter.com

The author is employed by Baxter Healthcare, a manufacturer of elastomeric infusion devices.

DOI 10.2146/ajhp130186

Assays for biological agents

We read with concern the study by Goldspiel and colleagues,[1] which evaluated the stability of alemtuzumab after storage at room temperature. The authors used high-performance liquid chromatography (HPLC) to assess the loss of alemtuzumab over time. It is essential to recognize that the pharmacologic properties of proteins, monoclonal antibodies, and other large molecules depend on molecular configuration and that varying storage conditions can alter that configuration and render the molecule biologically inactive. In order to assess the effect of varying storage conditions on these types of products for the purpose of extending expiration dating, it is essential that biological activity—not simply concentration—be assayed. HPLC may assess the quantity of a particular agent in a sample, but it will not detect differences in molecular configuration that can determine activity.[2] In our study,[3] referenced by Goldspiel et al., we found that alemtuzumab retained its biological activity over a wide range of conditions. It is entirely likely that storage at room temperature will not reduce activity, but until a confirmatory study is conducted using a measure of biological activity (e.g., flow cytometry), the findings of Goldspiel et al. should be viewed with caution.

The publication of a biological stability study using HPLC raises an important issue that we believe should be addressed by *AJHP*. Goldspiel et al. followed *AJHP*'s recommendations for evaluating drug stability, as put forth by Trissel[4] in 1983, before the widespread use of modern analytic techniques designed to detect biological activity. While Trissel's advice related to study design remains current and important, the analytic methods he recommended in 1983 are outdated and not applicable to biological products. The current standard for analytic assays of monoclonal antibodies are functional—most commonly immunoassays, including enzyme-linked immunosorbent assays.[2,5]

Biological agents represent a large proportion of hospital drug expenditures and typically have short expiration dates, resulting in waste and unnecessary expenditures.[6] Our previous work in establishing extended expiration dating for biological agents suggests that substantial savings are possible through waste reduction.[2,7-9] Given the increase in the number and cost of biological products and the unique challenges that they pose when attempting to demonstrate extended expiration dating, it is imperative that *AJHP* pursue new standards and guidelines for this work.

1. Goldspiel JT, Goldspiel BR, Grimes GJ et al. Stability of alemtuzumab solutions at room temperature. *Am J Health-Syst Pharm.* 2013; 70:439-42.
2. Damen CW, Schellens JH, Beijnen JH. Bioanalytical methods for the quantification of therapeutic monoclonal antibodies and their application in clinical pharmacokinetic studies. *Hum Antibodies.* 2009; 18:47-73.
3. Vermeulen LC, Puffer EB, Hallam M et al. Stability of alemtuzumab for low-dose induction and test doses. *Am J Transplant.* 2009; 9:651-2.
4. Trissel LA. Avoiding common flaws in stability and compatibility studies of injectable drugs. *Am J Health-Syst Pharm.* 1983; 40:1159-60.
5. Food and Drug Administration. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (accessed 2013 Mar 5).
6. Hoffman JM, Li E, Doloresco F et al. Projecting future drug expenditures—2012. *Am J Health-Syst Pharm.* 2012; 69:405-21.
7. Zhang Y, Vermeulen LC, Kolesar JM. Stability of stock and diluted rituximab. *Am J Health-Syst Pharm.* 2013; 70:436-8.
8. Ikeda R, Vermeulen LC, Lau E et al. Stability of infliximab in polyvinyl chloride bags. *Am J Health-Syst Pharm.* 2012; 69:1509-12.
9. Ikesue H, Vermeulen LC, Hoke R et al. Stability of cetuximab and panitumumab in glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm.* 2010; 67:223-6.

Jill M. Kolesar, Pharm.D., BCPS, FCCP, Professor
School of Pharmacy
University of Wisconsin
Madison, WI

Lee Vermeulen, B.S.Pharm., M.S., FCCP, Director
Center for Clinical Knowledge Management
UW Health
600 Highland Avenue
M/C 9475
Madison, WI 53792
lc.vermeulen@hosp.wisc.edu

The authors have declared no potential conflicts of interest.

DOI 10.2146/ajhp130128

Continued on page 1102

Letters

Continued from page 1101

We thank Dr. Kolesar and Mr. Vermeulen for their observation about potential differences in determining the stability of biological compounds versus simple chemical molecules. We agree that guidelines should be developed for conducting stability studies for biological agents that include a standardized method for determining biological activity and a definition of activity level that would be considered equivalent over time.

Justin T. Goldspiel, Undergraduate Student
University of Maryland
College Park, MD

Barry R. Goldspiel, Pharm.D., FASHP, Deputy Chief
Pharmacy Department
National Institutes of Health (NIH) Clinical Center
Building 10, Room 1C240, MSC 1196
Bethesda, MD 20892
bgoldspiel@nih.gov

George Grimes, B.S.Pharm., Chief
Pharmaceutical Development Service

Peng Yuan, Ph.D., Staff Scientist
Pharmaceutical Development Service

Gopal Potti, Ph.D., Supervisor
Analytical Unit
Pharmaceutical Development Service

Pharmacy Department
NIH Clinical Center
Bethesda, MD

At the time of writing, Mr. Goldspiel was a 2012 graduate of Poolesville High School, Poolesville, MD.

The authors have declared no potential conflicts of interest.

DOI 10.2146/130211

Editor's note: The AJHP *editors are investigating the establishment of standards for stability studies involving biological agents.*