NOTE

Development of an innovative delivery system for bacillus Calmette-Guérin bladder administration

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Purpose. To describe the development of an innovative process to deliver bacillus Calmette-Guérin (BCG) to an offsite urology clinic for bladder instillation.

Summary. The use of BCG, a live virus vaccine for treatment of patients with localized cancer of the urinary bladder, has created many logistical problems for hospitals and infusion center pharmacies. Due to its short stability, the drug cannot be made ahead of time and coordination with a patient's arrival at an infusion site is challenging. This becomes exceptionally challenging when a urology clinic has limited compounding capacity and/or is distant from the site of BCG medication preparation. This article describes an innovative process involving use of closed-system transfer devices (CSTDs) to allow for the administration of BCG in a urology clinic offsite from a medical center's infusion center facilities.

Conclusion. The use of the CSTD allowed the patients to continue to receive bladder instillations at an offsite urology clinic without significantly disrupting compounding workflow at the small infusion center pharmacy that was the nearest to the clinic.

Keywords: BCG, bladder cancer, bladder instillation, closed-system transfer device, infusion center, urology clinic

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The use of bacillus Calmette-Guérin (BCG), a live virus vaccine for treatment for recurrent tumors in patients with localized cancer of the urinary bladder, has created many logistical problems for hospitals and infusion center pharmacies. The virus has a short stability, 2 hours from reconstitution, and requires special handling for preparation and administration. Cross contamination of the virus with other preparations has been reported, necessitating extra precautions when preparing the virus.[1] The use of biological safety cabinets is necessary, and the cabinets require decontamination and cleaning after each BCG preparation session, a process that is time consuming and can be problematic in a busy infusion center with limited hood space for intravenous (IV) medication preparation.

Problem

At a large academic medical center, the urology services were geographically expanding as the institution acquired new clinics and integrated them into its cancer center. The practices had been providing, and wanted to continue to provide, BCG treatments, creating logistical problems for the pharmacy. A solution was needed in order to meet the safety requirements of BCG product preparation and delivery to patients within the limited timeframe of BCG stability.

For many of the medical center's urology clinics, the drug was being prepared in the main hospital's oncology pharmacy and delivered to the clinic site, typically just a few floors or a few blocks away. However, one of the urology clinics was located more than 20 miles from the main hospital

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in an area that often had significant traffic issues. Given the 2-hour stability of reconstituted BCG, the pharmacy was faced with limited options. The distance from the main hospital prohibited the mixing of BCG in the hospital's outpatient infusion pharmacy because of the challenge of consistently meeting the time requirements. A closer infusion pharmacy was available; however, that pharmacy was in a busy practice and only had one biological safety cabinet. Taking that cabinet out of service for cleaning and decontamination during the middle of the day would create significant burdens in terms of meeting the treatment needs of the cancer patients in that center. The pharmacy needed a new solution for delivery of BCG that would allow for advance preparation of the product without significant downtime for the IV hood. We began to look for a solution that would allow us to meet the needs of our patients while allowing them to stay at the remote urology center and, at the same time, meeting required regulatory standards.

The BCG preparation process in place at the time of the problem is outlined in Figure 1. The 11-step process involved placing reconstituted BCG in a syringe with a closed-system transfer device (CSTD), a drug transfer device attached via an adaptor to the end of a syringe that mechanically prohibits the transfer of environmental contaminants into a system and the escape of hazardous drug or vapor concentrations outside the system.[2] Once the BCG preparations for the day were mixed, the hood was cleaned and decontaminated and removed from use for at least 30 minutes. Intrathecal (IT) medications were never mixed in this hood (that prohibition served as an added precautionary measure), but the organization had the luxury of 6 hoods in total, so excluding this particular hood from use in preparation of IT medications was easy.

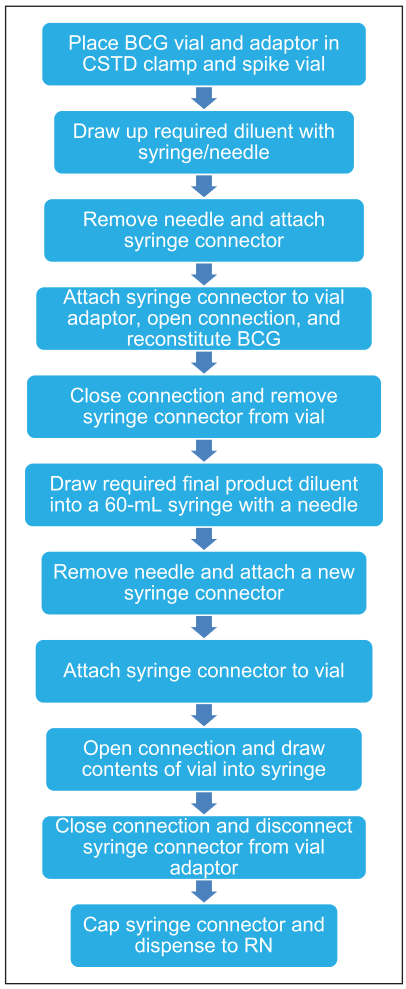
Solution

In discussions of potential solutions, the first thoughts were to use an infusion container system such as the Mini-Bag Plus (Baxter, Deerfield, IL) or ADD-Vantage system (Pfizer Inc., New York, NY). The problem was that BCG vials have an 11-mm top and none of the commercial systems at the time could handle the small vial size or, at least, handle it in a manner that would not introduce the possibility of exposing the preparer to BCG. One CSTD company offered a process to handle BCG, and we were already using that company's device; however, that process was for syringes only and required that the drug be already reconstituted and would not allow for transport over the distances required. The ideal solution was to find a process that would allow bedside activation of the vial while maintaining a closed environment. We worked with a medical device company (ICU Medical, San Clemente, CA), pharmacy technicians in the oncology pharmacy, pharmacists, and the urology clinic to develop, test, and evaluate a potential new device kit that might help overcome the BCG challenges. A second goal was to find a system that would maintain, if not improve, the efficiency of preparation while maintaining the safety standards and minimizing possible exposure.

KEY POINTS

- Bladder instillations of bacillus Calmette-Guérin (BCG) entail a complex process that poses significant logistical challenges for any cancer infusion center.
- Urology clinics that have limited compounding capacity and/or are located a significant distance from an infusion center are limited in their ability to provide BCG bladder instillation services due to safety concerns related to the drug's short stability timeframe.
- An innovative new process involving use of a closed-system transfer device was developed to overcome the logistic challenges of BCG administration in an offsite urology clinic.

Figure 1. Process for mixing bacillus Calmette-Guérin (BCG) preparations prior to the process change. CTSD indicates closed-system transfer device; RN, registered nurse.



New process. The solution developed included changing the delivery system from a syringe to an IV piggyback bag (50 mL) and creating a CSTD system process that would allow for the setup of the BCG vial in the pharmacy without reconstitution, allow for transport of the infusion setup (with the CSTD attached) to the urology clinic, and provide a process for BCG activation at the bedside, thereby delaying the 2-hour expiration window—all in a contained environment. The new process

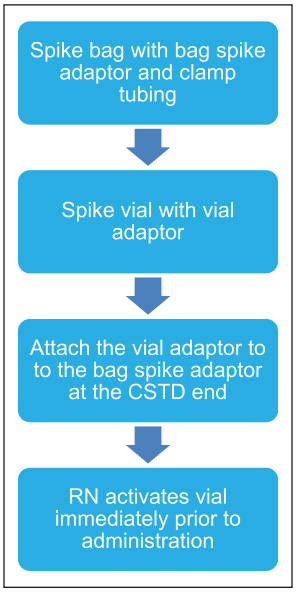
is outlined in Figure 2, and the system components are pictured in Figure 3. The process steps are as follows.

Step 1. The pharmacy technician attaches a CSTD bag spike adaptor with tubing (Figure 3) to the IV piggyback bag and clamps the tubing.

Step 2. A second CSTD vial adaptor (Figure 3) is placed on the BCG vial, and the 2 adaptors are connected to the opposite end of the tubing (Figure 4, panel A). The vial can be removed at the CSTD adaptor between the vial and the tubing. This setup can be delivered to the urology clinic in a zip-locked chemotherapy bag.

Step 3. At the appropriate time, a nurse removes the setup from the delivery bag and unclamps the tubing, creating an open connection between the IV bag and vial. The nurse then gently squeezes the IV bag, forcing fluid in the vial to reconstitute the BCG. After a short time to allow the powder to dissolve, the nurse then inverts the system and squeezes air into the vial, which forces the reconstituted BCG into the bag. The tubing is then clamped.

Figure 2. New process for mixing bacillus Calmette-Guérin (BCG) preparrations. CTSD indicates closed-system transfer device; RN, registered nurse.



Step 4. The vial is disconnected from the IV bag at the CSTD adaptor; this maintains a closed environment. The vial is disposed of in a biohazard container.

Step 5. The remaining IV bag with the mixed BCG has a CSTD adaptor and can be attached to the adaptor tubing, which is designed to deliver the solution to the bladder through a urinary catheter (Figure 4, panel B). The nurse inserts the urinary catheter adaptor into the urinary catheter and then attaches the BCG to the adaptor at the CSTD end. The nurse then opens the clamps, allowing the BCG to flow into the bladder by gravity.

The largest part of the time savings achieved through use of the new process resulted from pharmacy technicians preparing all of a day's BCG doses at once in the biologic safety cabinet. We still decontaminated the hood; however, the technician had to do this procedure only once a day, usually early in the morning before the infusion clinic became busy.

Testing for contamination. There was still concern that the activation of the bags in the IV hood could create a possibility of BCG contamination, so clinical epidemiology personnel were contacted to test the hoods for contamination. A pharmacy technician cleaned and decontaminated the IV hood as per the usual process, then prepared a dose of BCG using the new methodology. The

Figure 3. Components of the kits developed by ICU Medical to accommodate a new process for mixing bacillus Calmette-Guérin preparations that involves use of its ChemoClave and ChemoLock closed-system transfer devices. Kit #CH3507 is a ChemoClave-based system, and Kit #CL3927 is a ChemoLock-based system. Photos courtesy of and used with permission of ICU Medical, San Clemente, CA.

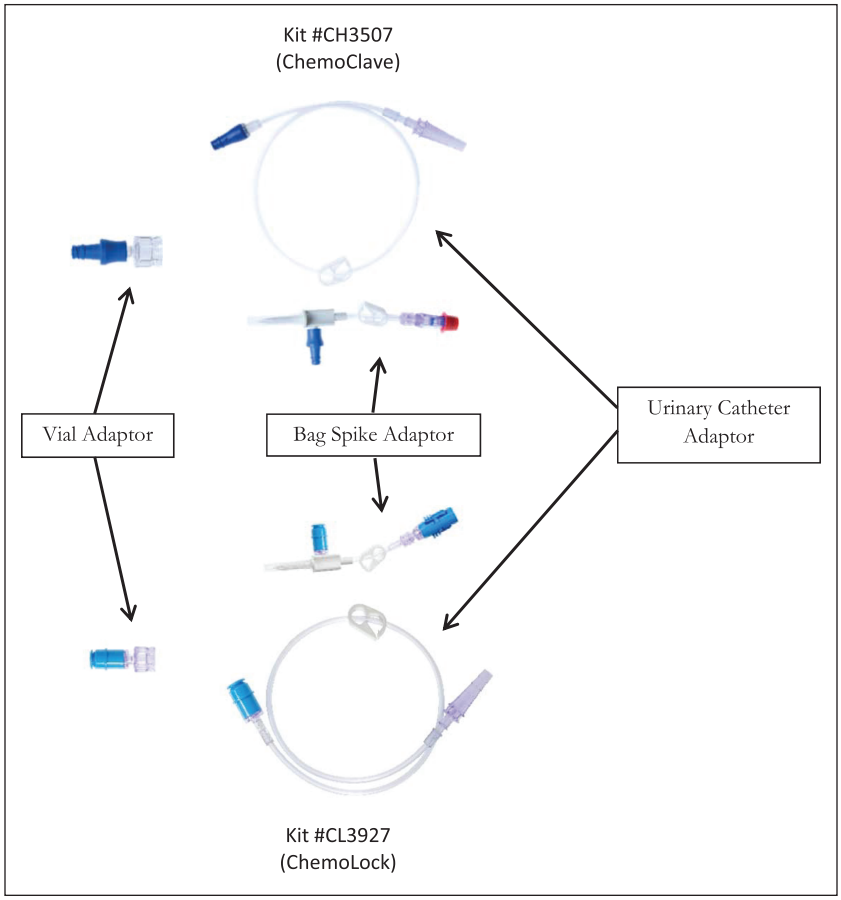
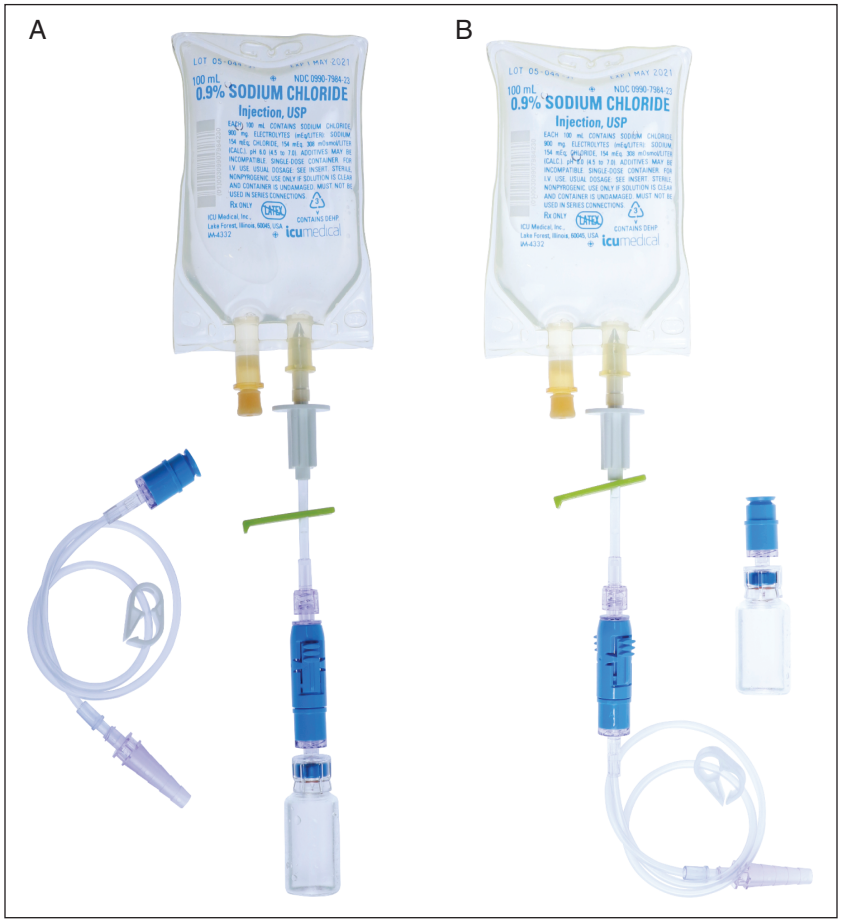


Figure 4. Setup for bladder instillation of bacillus Calmette-Guérin as it looks when ready for dispensing from the pharmacy (panel A) and as it appears with urinary catheter adaptor attached (panel B), just prior to administration. A sample medication vial used for training purposes and the ChemoLock closed-system transfer device (ICU Medical, San Clemente, CA) are shown. Photos courtesy of and used with permission of ICU Medical.



epidemiology department sampled the hood for surface and airborne contamination and tested for growth of BCG. No growth of BCG was detected.

One rationale for the new process was that BCG preparation could be handled by the nearest oncology infusion center, without the need to take an IV hood out of service for an extended time; and although that is not currently done, it is believed that the vials could be safely set up and activated in the urology clinic at the bedside.

Day-to-day process. Under the new process, the oncology pharmacies get a list of all patients due to receive BCG on a given day at one of the urology clinics. The BCG administration system can be set up in advance and delivered to the urology clinic for activation. The preparation time for the 2 different processes was measured, and pharmacy technician time was reduced by the new process (Figure 5). While the reduction in technician time for each dose is minimal, the new process provides major cumulative time savings, in that the chemotherapy hood is only used once per day, generally at the very beginning of the day, and is decontaminated once a day, thereby obviating the need to take the hood out of service multiple times per day. In a site with a single chemotherapy hood, this is a significant advantage. Once connected in the IV hood, the setup is assigned a 6-hour beyond-use date. Any unused doses are returned to the pharmacy to be properly disposed of at the end of the day or after a patient has left the clinic. This can be a problem in a time of shortage, so balancing the number of doses prepared in advance with those potentially wasted is a challenge.

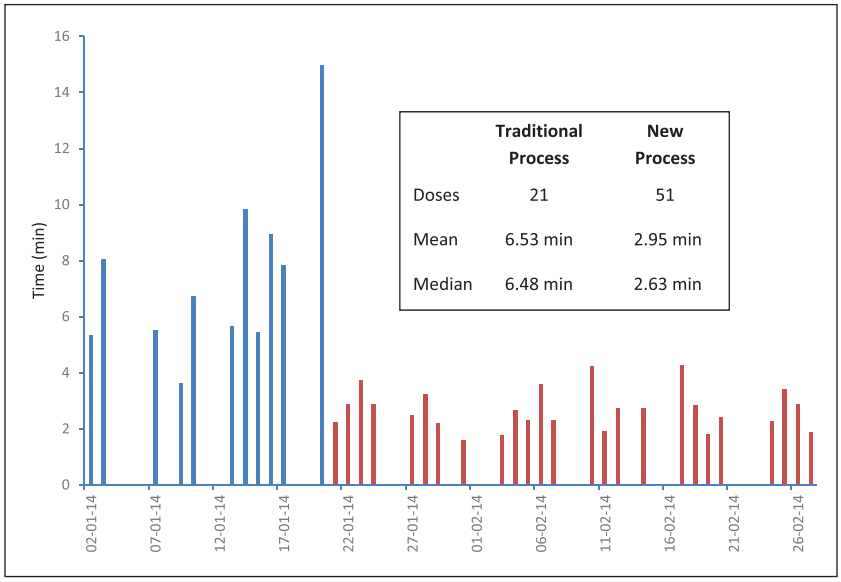
Discussion

Working with a CSTD device company, the cancer center developed a process to set up BCG in the pharmacy without reconstituting the vial. This process allowed for safe transport of the vial to a distant urology clinic for onsite activation and use. The process provided a safe setup method without exposing a pharmacy technician to BCG, as demonstrated by the lack of BCG detected in the IV hood. This process was used successfully and led ICU Medical to develop 2 kits (one version compatible with its ChemoClave CSTD and the other compatible with its ChemoLock CSTD; see Figure 3) for use with BCG preparations. This new process allows BCG activation at the bedside, thereby allowing pharmacy personnel to prepare the medication in advance without the limitation of the 2-hour stability. At our facility this process worked only when full vials were used to prepare a dose; any partial doses still had to be mixed according to conventional methods. This process dramatically improved the workflow of oncology infusion centers in providing BCG infusions to urology clinic patients while also maintaining safety.

Given the closed nature of the process, it is felt that the process could be applied in the urology clinics. The vials, IV bags, and CSTD kit required for BCG administration could be stored in an automated dispensing cabinet, and a nurse could activate the product just prior to use; this would be similar to the activation of IV products using the ADD-Vantage, Mini-Bag Plus, or similar systems. The simplicity of the method developed might allow other CSTD companies to develop similar kits.

One consideration in potential implementation of the new process is the effect of sterile compounding

Figure 5. Mean and median pharmacy technician time required to prepare a dose of bacillus Calmette-Guérin for bladder instillation with use of the traditional process (blue bars) and the new process (orange bars).



requirements specified in *United States Pharmacopeia* (USP) general chapter 797[3] and hazardous drug handling requirements specified in USP general chapter 800 (<USP 800>).[4] We believe that if the components of the BCG delivery system are assembled under a hood but the drug is not reconstituted, such a process might at least meet the stability standard applicable when accessing a single-dose vial, which would give a beyond-use date of 6 hours. Once reconstituted using the process, the stability is that of the drug: 2 hours. From a USP <800> perspective, the assembled product would be a closed system. Could it then be considered to meet the standard of a conveniently packaged product, meaning that a risk assessment could be done and the institution could determine the personal protection equipment required for mixing and administering the product? If companies would do the right studies and submit them for Food and Drug Administration approval, could this system be comparable to other systems that allow mixing on patient care units? Even if not, imagine the benefit if the stability of the assembled (but unreconstituted) products could be multiple days or even weeks. This extended stability window would also help in times of shortage by allowing more flexibility in prepreparing doses, which could be done with the knowledge that if doses were not used the same day, they might be used later. Until more is known about how regulators will view this type of innovative solution to a complex problem, there are more questions than answers and thus there can be no "official" recommendations. Pharmacy leaders at each practice site will have to assess how they would approach using this process.

BCG causes significant problems in compounding, especially at smaller sites with limited chemotherapy hood capacity and sites that are far enough away that the 2-hour stability window limits mixing and delivering of the drug. Even though the new process does not yield a major time savings per individual compound, it can yield considerable time savings overall because of the decreased time an IV hood is unusable due to decontamination. Since the preparations are prepared early in the day all at once, the chemotherapy hood is only out of service for a single decontamination process; this is a significant advantage in infusion centers that have limited hood space and are associated with busy infusion centers and urology clinics. While a movable glove box could provide an answer in some of these cases, at our practice site it was decided that buying a glove box, setting it up in a urology clinic, and sending a pharmacist or pharmacy technician to the clinic for a small number of patients each week would be inefficient and that a more practical approach was to use the process described here.

Conclusion

The new process allows cancer centers to meet patient needs by supplying BCG preparations for administration in offsite local urology clinics in a safe and effective manner. This innovative process, which provides a solution to a complex problem, was developed through collaboration of an oncology pharmacy, a device company, and urology clinics.

Disclosures

The authors have declared no potential conflicts of interest.

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