Botulinum Toxin Temperature Stability

Many customers like you have questions about how best to store their botulinum toxins: if they should be refrigerated, if they can be frozen, and if they can be left at room temperature. If you are storing Botox or other botulinum toxins for future use, or if you are wondering whether your product is still stable and effective after being left at room temperature, this information should help.

Botox

Stability in Storage

Botox is the most popular botulinum toxin, and extensive studies have looked into not only its safety and use but also its temperature stability. According to its manufacturer, Allergan, you should store Botox in a refrigerator (between 2° C and 8° C) or in the freezer (below -5° C). This should give the toxin a shelf life of 36 months from the date it was manufactured. Although you can safely store your Botox in the freezer, extremely low temperatures (below -60° C) could affect the vial's rubber stopper, losing the vacuum seal and affecting the product's sterility. A case study after accidental freezing drugs, including Botox, for more than four hours (http://www.pharmacytimes.com/publications/health-system-edition/2016/january2016/high-value-medications-preserving-value-after-a-frosty-flounder) confirmed that, according to Allergan, this freezing would not affect the drug's potency, constitution, and safety.

Stability During Shipping

Although you may follow storage directions within your clinic, you may be concerned about what happens to your Botox before it arrives. For your peace of mind, we do ship your botulinum toxin using a special thermo-regulated packages, ice packs, and extra cushioning to keep them safe and cool for about ten days while they are en route to you. However, there may be the occasional shipping delay due to weather, high volumes, or other issues with the shipping company, or there may be a heat wave or cold snap in your area. You may be concerned if your package arrives after ten days, or if ambient temperatures were unusually high recently, but there is no need for alarm.

A study by Cohen *et al.*, published in the *American Journal of Health-System Pharmacy* in 2007 (http://www.medscape.com/viewarticle/562416_3, http://www.ajhp.org/content/64/16/1711), looked at the effect of leaving refrigerated medications, including Botox, at room temperature. This may occur during transit, during a power outage, or simply when someone accidentally leaves a temperature-sensitive drug on the counter. Allergan told the study authors Botox is stable up to five days at room temperature, which means that even if your refrigerator quits working over the weekend, or someone accidentally leaves a box out, the Botox should be fine. When authors of another study referenced available product information and contacted manufacturers directly, they discovered Botox does remain stable at 25° C up to 14 days or at 30° C up to 7 days (http://www.elsevier.es/en-revista-farmacia-hospitalaria-english-edition--221-articulo-thermolabile-drugs-operating-procedure-in-S2173508511000141, http://www.grupoaran.com/mrmUpdate/lecturaPDFfromXML.asp?IdArt=456848&TO=RVN&Eng=0). These temperatures represent more extreme shipping and storage conditions than usual. Even if your package does not arrive cool, it should be safe and effective to use.

Stability After Reconstitution

You may find it quicker and easier to reconstitute your Botox well before a treatment, and this is possible to do while retaining the product's viability. After you add saline solution to a Botox vial, assuming the seal is intact and the vacuum has sucked in the solution, the reconstituted Botox should remain stable in the refrigerator (2° to 8° C) up to 24 hours, according to the manufacturer. It should then still be safe and effective to use on your patient. This is in contrast to the product's package insert, which says you should use the reconstituted Botox within four hours. Assuming you rest the reconstituted Botox in the refrigerator, it should be safe and effective the next day.

However, it seems Allergan may be playing it safe with their stability recommendations. According to other studies, Botox may remain effective a month or longer after reconstitution. In one study by Mee Young Park and Ki Young Ahn in the *Journal of Clinical Neurology* (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3722467/) July 2013, researchers examined the effectiveness of Botox two hours, 72 hours, and one, two, three, and four weeks after reconstitution with unpreserved saline. For this study, the researchers compared the effectiveness of freshly-reconstituted Botox to older, refrigerated Botox by injecting each into a different foot of 94 volunteers affected by extensor digitorum brevis (EDB) muscle paralysis. The scientists measured the compound muscle action potential (CMAP) amplitude and area one week, 12 weeks, and 16 weeks after injection to determine if the injection worked.

What the researchers discovered was surprising. Although there tended to be increased CMAP amplitude and area 12 and 16 weeks after the injection, the effects of all the differently-stored Botox solutions were statistically similar. No matter if the Botox was fresh or stored for three days or one to four weeks, it seemed to be just as effective at treating the muscle. Although some practitioners may dispose of Botox that has been sitting reconstituted in the refrigerator longer than a few hours, this study suggests it may remain stable up to four weeks. Disposing of the Botox can be wasteful of time and money, but knowing it can be used up to about a month later could help practitioners reduce waste and be more convenient for clinics who want to prepare the solution in advance.

This was not the only study to suggest reconstituted Botox is still effective much longer than the manufacturer suggests. Hexsel DM *et al.* published a study in *Dermatological Surgery* in May 2003 examining the effectiveness of older Botox for treating glabellar furrows. They started by reconstituting Botox with preservative-free saline and refrigerating the solution at the recommended 4° C. There were seven batches of Botox, prepared freshly and every week for six weeks, making the oldest Botox 43 days old. 85 patients randomly received treatment with one of the seven batches then were assessed by physicians, independent observers, and themselves during a four-month follow-up period. The mean time muscle function returned was 75 days after treatment, and by four months, most had reached baseline levels. Although Botox is only supposed to remain effective four hours after reconstitution, all solutions, up to 43 days old, seemed to have statistically similar results and duration. These two studies seem to support that you can use your reconstituted, refrigerated Botox up to a month or month-and-a-half later. This can be an advantage especially to clinics who use low volumes of Botox, minimizing waste, and to busy clinics who wish to prepare the solution in advance.

It is best not to agitate Botox after reconstitution (http://www.intl.elsevierhealth.com/media/us/samplechapters/9780723433491/9780723433491.pdf) because this could denature the toxin and reduce its duration. Otherwise, it seems you may be able to keep your reconstituted Botox in the refrigerator weeks before use as it maintains its effectiveness and duration.

Xeomin (Bocouture)

Stability in Storage

Xeomin, and its cosmetic version Bocouture, are popular botulinum toxins made by Merz Pharma. These botulinum toxins differ from Botox in that they are free of complexing proteins and are stored at room temperature, not in the refrigerator. While there may be speculation whether the complexing proteins found in Botox and other botulinum toxins add some stability during storage, studies suggest the proteins do not affect the active neurotoxin's diffusion or enhance product stability while in storage (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010823/).

According to the manufacturer's product leaflet, you can store the botulinum toxin at room temperature, up to 25° C, if unopened. The product is supposed to remain effective up until the expiry date at those temperatures. The manufacturer (http://www.xeomin.com/physicians/about-xeomin/reconstitution-storage/) says the botulinum toxin should be fine up to 36 months from the manufacture date if stored at room temperature, refrigerated (2° C to 8° C), or in the freezer (-20° C to -10° C).

Similar to Allergan, it seems Merz may be playing it safe with their storage recommendations. Studies have suggested (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010823/) you can store Xeomin longer, and at more stressful temperatures, than you might think. Researchers discovered that even after leaving Xeomin for 48 months at room temperature or in a refrigerator, which is a temperature range between 5° C and 25° C, its neurotoxin, sucrose, and human serum albumin content remained the same and its neurotoxin's biologic activity remained effective. This means Xeomin remains stable one year longer than the manufacturer says, and it remains stable without requiring refrigeration, unlike other botulinum toxin brands.

Stability During Shipping

Although Xeomin does not need refrigeration before reconstitution, and therefore does not need refrigeration during shipping, studies discovered Xeomin can withstand more extreme temperatures than what it would usually encounter. The botulinum toxin remained stable after storage for 18 months at 30° C and at least six months at 40° C. Even at 60° C for a month, the Xeomin remained within the release specifications, so it could still be effective. At an even bigger extreme, 80° C, the neurotoxin's activity reduced within five days, but the protein activity did not fall below more than a third after 10 days (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010823/). Although storage at these temperatures is not ideal, research suggests even if the product was left in a vehicle on a hot day, if would remain just as effective as if it was kept at room temperature.

Stability After Reconstitution

According to Merz, after reconstituting your Xeomin or Bocouture, you should place it in the refrigerator (2° C to 8° C). It can remain there up to 24 hours before use. Although studies have not looked into Xeomin at the same depth as they have analyzed Botox, some doctors still use Xeomin up to two weeks after the solution is prepared (https://www.realself.com/question/xeomin-potency-after-mixing).

One particular study by Soares *et al.*, published June 2015 in the journal *Dermatologic Surgery*, looked into the effectiveness of reconstituted Xeomin stored at room temperature (25° C) for one week. There seemed to be no statistical difference in the effectiveness or duration of the room-temperature Xeomin

versus the freshly-prepared Xeomin. This seems to suggest even after reconstitution the product may be safely stored at room temperature.

Dysport (Azzalure)

Stability in Storage

Dysport, along with its cosmetic version Azzalure, is another boutlinum toxin type A, this one made by Ipsen. According to its product leaflet, you should store unopened Dysport powder in a refrigerator (2° C to 8° C). Under these conditions, it should remain stable and effective for 24 months after its manufacture date. The product leaflet states you should not freeze Dysport, so storage in the freezer is not an option.

Dysport is not as extensively-studied as Botox as far as use after storage in the refrigerator or at room temperature. However, in one particular study (http://www.elsevier.es/en-revista-farmacia-hospitalaria-english-edition--221-articulo-thermolabile-drugs-operating-procedure-in-S2173508511000141, http://www.grupoaran.com/mrmUpdate/lecturaPDFfromXML.asp?IdArt=456848&TO=RVN&Eng=0), the authors referenced product information and contacted manufacturers directly about leaving drugs at room temperature. According to the researchers' sources, Dysport will still be effective and safe to use even after three days at room temperature, up to 25° C. An accidental weekend on the counter may not be detrimental to your botulinum toxin after all.

Stability During Shipping

For your peace of mind, we ship Dysport and Azzalure in thermo-regulated packaging with ice packs and extra cushioning. This should keep the temperature stable during shipping for at least ten days. However, even for three days at room temperature, your Dysport should be fine (http://www.elsevier.es/en-revista-farmacia-hospitalaria-english-edition--221-articulo-thermolabile-drugs-operating-procedure-in-S2173508511000141, http://www.grupoaran.com/mrmUpdate/lecturaPDFfromXML.asp?IdArt=456848&TO=RVN&Eng=0).

Stability After Reconstitution

According to the Dysport product leaflet, after you reconstitute the powder with saline, you can store it up to 8 or even 24 hours in the refrigerator (2° C to 8° C) before use (http://ipsen.ca/wp-content/uploads/2017/01/Dysport-therapeutic-pm-Jan-3_17.pdf). The manufacturer does not recommend freezing reconstituted Dysport. It is best not to agitate the Dysport solution after reconstitution (http://www.intl.elsevierhealth.com/media/us/samplechapters/9780723433491/9780723433491.pdf) since that action could denature the toxin and reduce its duration. Dysport is not as extensively-studied as Botox as far as use long after reconstitution.

Myobloc (Neurobloc)

Stability in Storage

Myobloc, also called Neurobloc in some areas, is a botulinum toxin made by Eisai. This particular product is made of botulinum toxin type B, as opposed to the others which are made of type A, but both types have similar action on muscles. The Myobloc product leaflet recommends storing this botulinum

toxin in the refrigerator (2° C to 8° C) (http://journal-dl.com/downloadpdf/591087c43fbb6e13743a76b6). However, it is also possible to remove the Myobloc from the refrigerator and store it at room temperature (below 25° C) up to three months. After this time, the manufacturer says you should not place the product back in the refrigerator. The product leaflet says not to allow the Myobloc to freeze, so freezer storage is not an option.

Despite the manufacturer's recommendation to keep the product at room temperature only up to three months, research suggests it remains stable up to nine months (http://journal-dl.com/downloadpdf/591087c43fbb6e13743a76b6). Not only that, it remains stable up to 21 months in the refrigerator according to the manufacturer (https://www.departures.com/lifestyle/health/botox-or-bust), or up to three years at 2° to 8° C according to some research (https://books.google.ca/books?id=yxArDwAAQBAJ&pg=PT74&lpg=PT74&dq=myobloc+stable+at+room+temperature+for+up+to+9+months&source=bl&ots=Zm3JO7LJM5&sig=elrzRiKAU1Y4G__fzQXRf2ugAyw&hl=en&sa=X&ved=0ahUKEwiV_OKj_OvVAhUL5IMKHUZfBfgQ6AEIJjAA#v=onepage&q=myobloc%20stable%20at%20room%20temperature%20for%20up%20to%209%20months&f=false). Evidence suggests You can refrigerate Myobloc for 21 months, then store it at room temperature for six months, then move it to 4° C. Even if you dilute Myobloc up to sixfold with saline, it can remain potent for at least 24 hours at room temperature. It seems you may have even more storage options for your Myobloc or Neurobloc than you previously thought.

Stability During Shipping

Although Myobloc can spend time out of the refrigerator, for your peace of mind, we ship your products in thermo-regulated packaging with ice packs and extra cushioning. However, the botulinum toxin may be fine up to nine months (http://journal-dl.com/downloadpdf/591087c43fbb6e13743a76b6) with refrigeration, according to researchers, so even if shipping is delayed, it should still be effective and safe to use.

Stability after Reconstitution

Myobloc and Neurobloc are already in solution, so no reconstitution is needed.

Summary

Studies of Botox and other botulinum toxins seem to suggest they remain viable in storage long past the manufacturer's recommendations, even after reconstitution. However, each botulinum toxin differs from the others, so you should look at the shelf life of each brand separately and trust reliable studies for your information.

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