Even the best-laid pharmaceutical product transportation plans can be derailed by events outside of your control. When a drug product is exposed to temperatures outside of the acceptable range, an “excursion” has occurred. This brief advises what to do when an excursion occurs, and how to evaluate its consequences from a quality and regulatory compliance perspective.

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The transportation and storage of pharmaceutical products are regulated by Good Manufacturing Practices (GMPs) to ensure that the pharmaceuticals are protected from environmental hazards such as extremes in temperature and humidity.

However, even the best-laid product transportation plans can be interrupted by Mother Nature, quirky software, electrical surges, schedule changes and mechanical variances. When a product is exposed to temperatures outside of its acceptable range, an “excursion” has occurred. This event can potentially threaten the integrity of the product.

This article will look at what to do when an excursion occurs, and how to evaluate its consequences from a quality and regulatory compliance perspective.

For the purposes of this article, “product” can include raw materials and intermediates, bulk drugs, and filled/finished/packaged pharmaceutical and biological products. Likewise, “transport” encompasses the movement of product both internally (from manufacturing site to manufacturing site) and by external partners such as freight forwarders, trucking companies, and air, ocean, and train carriers.

Once the product reaches the first paying customer, such as a wholesaler, pharmacy, or clinical facility, the responsibility for its satisfactory handling is turned over to that entity, which must then ensure the product’s integrity through to the patient.

**Temperature specifications:** Products are stored according to label storage conditions as registered in the regulatory filing of the product. However, the allowable temperature range during transportation may be wider than the labeled storage conditions when supported by known stability data. This data, or “stability profile,” paints a time and temperature picture for the safe handling of the product. Materials that are known or suspected to be adversely affected by temperatures outside label storage conditions are known as “temperature-sensitive” products. Examples include a vaccine labeled for 2°C to 8°C storage that is adversely affected by freezing, or a antibiotic labeled for storage below 25°C that is adversely affected at temperatures above 37°C.

The regulatory organizations at the sending and receiving locations should agree to any allowable deviations from the label storage conditions, and the supporting data.
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should be appropriately specified in shipping and receiving site procedures. The regulatory filings for the product at both the origin and destination locations should reflect shipper’s deviations. Where appropriate, the standard operating procedures (SOPs) should document those approved transport temperature conditions.

- **Temperature control:** Protecting temperature-sensitive products from temperature excursions requires the use of specialized packaging during storage and transit. This packaging may be passive (such as an insulated container), or active (such as a refrigerated storage unit). The purpose of the packaging is to ensure that shipment contents are protected from ambient conditions expected to be encountered in the transport lane (in other words, during shipping). This reduces the risk of product temperature excursions. The responsible quality departments at both the sending and receiving sites must agree on the mechanism to be used for thermal protection of the material while en route.

- **Temperature monitoring:** The successful performance of thermal packaging can be documented through the use of temperature monitors—devices that record and store temperature data. When appropriate, internal distribution should utilize single or multiple temperature monitors to record the transportation temperature of the load. As much as possible, the monitor(s) should capture data that represent either the product itself or the worst-case product exposure, as opposed to monitoring the surrounding space exclusively.

  The number, type and placement of temperature monitors should be based upon the risk assigned during evaluation of the shipping lane, taking into consideration:

  - The thermal sensitivity of the product versus the expected ambient temperatures to be encountered
  - The duration of transit
  - The value of the product in the load
  - The expectations of the sender and receiver
  - Local regulatory requirements
  - Product filing requirements

  If a product has a product stability profile, a temperature monitor should be used to determine if those parameters were met while the material was in transit. Care should be taken to prevent inaccurate readings.

  In addition to monitoring and storing temperature data during transit, a simpler temperature-indicating device can be used for external distribution to the first paying customer. While this type of device doesn’t provide data on the full temperature exposure over time, it indicates whether the product was protected from a specific threshold event, such as freezing. The decision to use a temperature-indicating device for external deliveries should be based upon the requirements of the customer and local regulatory agencies, the value and thermal sensitivity of the product, the mechanism used for thermal protection, and the duration of transit to the customer.

- **Reporting and evaluating excursions:** Any excursions outside of allowable transport temperature conditions, as defined in the stability profile for the product, should be reported back to the person at the release site responsible for quality. The impacted product must be placed in a restricted status—either physically or electronically—while the quality department determines if the temperature excursion had any potential impact on product integrity. Care should be taken to ensure that not only are the chemical attributes of the product intact, but also that the physical and biological immunological behavior is unaffected.

  An assessment should be made using the duration of the excursion time and the extent of temperature
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deviation compared to specific product stability data or stability statements issued by the quality department. Such data may be derived from accelerated and long-term stability studies, forced degradation studies, temperature cycle studies and freeze/thaw studies.

- **Customer reports:** In general, temperature excursions reported by customers, such as hospitals or pharmacies, should not be evaluated against stability data if there is a lack of specific time and temperature records. This is because of the potential risk of decisions being made based on unsubstantiated data. However, the quality department may evaluate the excursion where there are sufficient records to substantiate the excursions, and to support a usage or further distribution decision.

- **Additional testing:** Depending upon the product, its regulatory filing, and the requirements of the countries it is shipping from and to, it may be possible to perform additional testing to determine if the excursion had any impact on product quality. The decision to test, and the conclusions drawn based on test results, should be made by the quality department on a case-by-case basis. Test results should be compared to the original release testing and, using the degradation profile of the product, be extrapolated to the product’s expiration date.

- **Product disposition:** Upon completing an assessment of the excursion’s impact on product integrity, the quality department must determine the disposition of the affected product. Partial release may be considered, but only when part of a batch is not impacted by the excursion, and documentation is available to allow clear segregation of product that has been transported within the defined transit temperature range.

- **Compliance improvement:** In addition to the quality assessment, an investigation should take place to determine the root cause of the temperature excursion, and whether preventative actions are warranted. Temperature excursion occurrences should be trended, which may help identify problem areas as well as corrective steps. For example, trends may be identified with a specific site, carrier, transport lane, day of the week, season, type of thermal protection, or load configuration.

The best way to handle temperature excursions during the transportation and storage of pharmaceuticals is with planning and prevention. Developing a detailed standard operating procedure for handling temperature-sensitive products with internal manufacturing departments, as well as with external partners, will cut the risk during product movement. Working with experienced materials-handling professionals who can initiate risk-mitigation activities ahead of time will be the best defense against temperature excursions.
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