Comparative Stability of Three Epinephrine Products Under Extreme Temperature Conditions

Presentation ID: L32

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RATIONALE

- Epinephrine is the first-line treatment for severe allergic reactions, including anaphylaxis. Despite epinephrine's well documented history of safety and efficacy, patients/caregivers frequently fail to treat or delay treating severe allergic reactions, among the most common reasons for the lack of treatment compliance are concerns about carrying/transporting epinephrine auto-injectors.[1,2]
- *neffy* is an intranasal (IN) epinephrine spray being developed for the emergency treatment of (Type I) allergic reactions, including anaphylaxis**.** *neffy's* pharmacokinetic and pharmacodynamic profiles have been repeatedly demonstrated to be within the range of approved injection and it is anticipated that *neffy* will provide a safe and effective treatment option, particularly for patients/caregivers who are reluctant to use injectable devices.
- Given the critical importance of early treatment, at-risk patients are instructed to always carry epinephrine auto-injectors, regardless of environmental conditions, with the understanding that the products may be exposed to extreme ranges of temperature conditions, such as being left in a hot car.
- Previous long-term room temperature stability research demonstrated *neffy* was within regulatory specifications for more than 24 months at 25˚C (77˚F).
- The current study was conducted to evaluate the influence of extreme temperature conditions on the potency of three different epinephrine product formulations: *neffy* (epinephrine nasal spray; ARS Pharma); EpiPen (Viatris); and Symjepi (Adamis Pharma).

METHODS

- Stability data was collected on epinephrine's potency (assay) from the three products: *neffy*; EpiPen; and Symjepi. Extreme temperature stability was assessed at 50˚C (122˚F) [car temperature] for 3 months and 40˚C (104˚F) for 6-months. Reference stability was conducted at room temperature testing conditions 25˚C (77˚F).
- Validated Reverse phase high-performance liquid chromatography methods were used to determine the epinephrine assay purity of all formulations.
- Regulatory shelf-life specifications for epinephrine products allow for up to a 20% decline in potency.

RESULTS

CHANGES in POTENCY UNDER ROOM TEMPERATURE CONDITIONS (Table 1 & Figure 1)

Comparative potency for all products, across room temperature conditions (25˚C/77˚F) is provided in **Table 1** and in **Figure 1.** The epinephrine potency changes over 6-months at 25˚C/60% RH is as follows: -10.0% (Symjepi), -7.7% (neffy), -4.9% (EpiPen).

CHANGES in POTENCY UNDER EXTREME TEMPERATURE CONDITIONS (Table 1 & Figures 2, 3)

Comparative potency for all products, across two extreme temperature conditions (40˚C/104˚F), and (50˚C/122˚F) are provided in **Table 1**, and in **Figure 2** (40˚C), and **Figure 3** (50˚C).

The epinephrine potency changes over 6-months at 40˚C/75% RH were as follows:

- -27.5% (EpiPen),
- -17.2% (Symjepi),
- -13.9% *(neffy*)

The epinephrine potency changes over 3-months at 50˚C were as follows:

- -56.6% (Symjepi),
- -41.6% (EpiPen),
- -8.6% (*neffy*)

CONCLUSIONS

neffy was more stable than injection products and remained within shelf-life specifications for potency even after 3-months under extreme temperature conditions (50˚C) and 6-months at 40˚C. EpiPen and Symjepi showed rapid and extensive degradation and were subpotent at these extreme temperature conditions after a short period of time.

The expiration period for injection products is 18-months, while *neffy*, a needle-free epinephrine alternative, is anticipated to be launched with an initial expiration period of 24-months. Under extreme temperature conditions , i.e., accidently being left in a vehicle on a hot day, *neffy*, unlike epinephrine auto-injectors does not raise concerns about potency and potential product failures.

neffy epinephrine nasal spray appears to have a longer shelf life and sustained stability under extreme conditions compared to injection products.

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Table 1: Comparative Potency by Temperature Condition

Duration	Assay % (25°C/60%RH)		
	Product		
	neffy	EpiPen	Symjepi
Initial	106.7	107.1	108.9
6 months	99.9	102.2	98.9
Duration	**Assay % (40°C/75%RH)**		
	Product		
	neffy	**EpiPen**	**Symjepi**
Initial	106.7	107.1	108.9
1 month	104.1	103.1	99.0
2 months	100.6	98.2	91.2
3 months	101.2	94.4	95.4
6 months	92.8	79.6	91.7
Duration	**Assay % (50°C)**		
	Product		
	neffy	**EpiPen**	**Symjepi**
Initial	106.7	107.1	108.9
0.233 month	104.2	104.5	105
0.5 month	103.6	101.5	96.1
1 month	102.6	96.7	79.2
2 months	98.1	81.4	54.7
3 months	99.0	65.5	52.3

Figure 1: Comparative Potency at 25°C

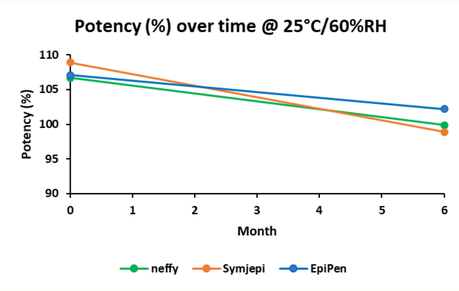


Figure 2: Comparative Potency at 40°C

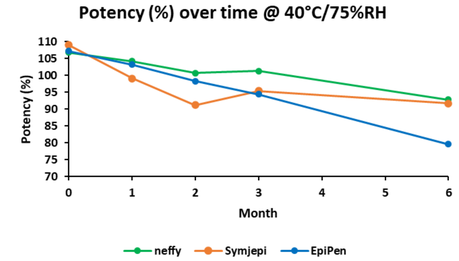
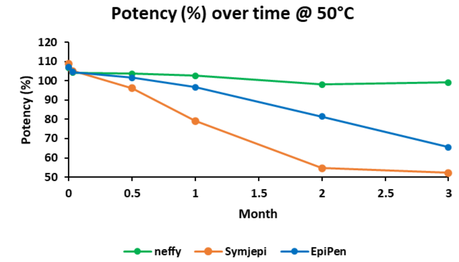


Figure 3: Comparative Potency at 50°C



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Presented at the Annual Scientific Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI); February 23 -26, 2024; Washington DC