### Relative Potency Factor Requirements

#### 1. Relative potency must be for the same effect.

#### 2. The potencies must be measured in the same bioassay.

#### 3. The agents must have the same efficacy for the measured effect.

#### 4. The agents should have parallel dose response curves for the measured effect.

### FDA's Relative Potency Approach

1. The mid-range dose of each drug used as a "vasopressor" was chosen as an equi potency dose for an effect never measured.
2. Comparisons were made of the hemodynamic effects of two agents from different bioassays.
3. The agents compared have different efficacies for cardiovascular effects.
4. The agents do not have parallel dose response curves for the measured effect.

### Adverse Cardiovascular Events

- **Ephedrine:**
  - Heart Rate
  - Blood Pressure

- **Epinephrine:**
  - Heart Rate
  - Blood Pressure

### Ephedrines Alkaloids (Botanical/Raw)

#### Oral Dosing

- **Heart Rate:**
  - Blood Pressure

### Ephedrine (Synthetic)

#### Oral Dosing

- **Heart Rate:**
  - Blood Pressure

### Epinephrine (Synthetic)

#### Recommended Bolus Intravenous Dose Range

### Epinephrine: Phenylephrine = 65

- **Recommended Bolus Intravenous Dose Range:**
  - **Adverse Cardiovascular Events:**
  - **Baseline, endogenous epinephrine levels pose unacceptable risk of adverse cardiovascular events.**

### Implications of FDA's Relative Potency Approach

- There is no safe level of exercise.
- The level of epinephrine determined by FDA to cause adverse cardiovascular effects is less than the level of endogenous epinephrine created by moderate exercise and is considerably lower than that created by rigorous exercise. (Clutter et al. 1989)
- **NOAEL <<< NOEL for epinephrine**

- **Baseline, endogenous epinephrine levels pose unacceptable risk of adverse cardiovascular events.**

- **Corollary to point above.**

- **FDA's determination of a relative potency factor for epinephrine and phenylephrine presumes the drugs can be used interchangeably in clinical practice.**

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**Abstract**

Relative potency approaches for predicting the pharmacologic and toxicologic effects of similar chemicals have been applied in diverse areas of regulatory science, including environmental toxicology, risk assessment, pesticide regulation, and in drug efficacy and safety evaluation. The approaches assume that the chemicals to be assessed behave as if they were dilutions of a reference chemical producing a specific biologic response, and that some biologic differences between the assessed chemicals and the reference chemical are quantitative rather than qualitative. The validity of these assumptions directly determines whether applying a relative potency approach is valid in any particular situation. Traditionally, several criteria are evaluated to determine how well a group of chemicals conforms to the assumptions of the relative potency approach. These include that the chemicals are molecular congeners, exhibit similar patterns of metabolism and detoxification, exhibit parallel dose response curves for the specific effect of interest in the same biological assay, share the same molecular target of action, have similar mechanisms of action for the effect of interest, and exhibit parallel dose addition for the effect of interest when combined in a mixture. We used these criteria to evaluate a novel relative potency approach adopted by FDA for predicting adverse cardiac events of herbal ephedra. We found the approach unusual in several key aspects: It employs an indirect comparison of ephedra alkaloids to the reference compound ephedrine via a surrogate reference chemical, ephedrine; it assumes quantitative similarity based on potency for qualitatively dissimilar therapeutic indications, and; it employs recommended dose ranges for the quantitative comparison rather than dose response data. We discuss the validity of this novel approach for safety evaluation and its implications for future regulatory actions involving drugs and supplements.

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**References**

- Dose range of ephedrine sulfate for IV administration for blood pressure support is 5-25 mg (15 mg is the mid-range dose; 11.6 mg phenylephrine) for phenylephrine it is 0.1 - 0.18 mg/min (mid-range dose is 0.14 mg/min x 60 minutes = 8.4 mg/hr)
- If a comparison between mid-range vasopressor doses published for ephedrine and phenylephrine were used to calculate their relative potency, the ratio would be [per FDA's methodology]:
  - Ephedrine: Phenylephrine = 11.6 mg:8.4 mg = 1.4
  - i.e., Phenylephrine is 1.4 times more potent than ephedrine by this estimate.
- However, Saravanan et al. compared the minimum vasopressor dose for each drug in Caesarean section patients:
  - +3 mg ephedrine sulfate (77.13% ephedrine) 0.5329 mg phenylephrine
  - 3.4 mg ephedrine = 0.5329 mg phenylephrine
  - Ephedrine: Phenylephrine = 33.4 mg:0.5329 mg phenylephrine = 62.7
  - i.e., phenylephrine is 62.7 times more potent than ephedrine in the same bioassay (e.g., direct clinical comparison).

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**Relative Potency of Ephedrine to Phenylephrine Using FDA's Approach vs. Using Bioassay Data**

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**Table: Ephedrine vs. Phenylephrine**

<table>
<thead>
<tr>
<th>Ephedrine Alkaloids (Botanical/Raw)</th>
<th>Recommended Bolus Intravenous Dose Range</th>
<th>Relative Potency of Ephedrine vs. Epinephrine</th>
<th>( \text{Ephedrine} \times\text{Relative Potency} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Dosing</td>
<td><strong>Heart Rate Blood Pressure (Measured Effects)</strong></td>
<td><strong>Relative Potency of Ephedrine</strong> to Epinephrine = 0.05-0.25 ( \text{Ephedrine Equivalents} )</td>
<td>Heart Rate Blood Pressure (Measured Effects)</td>
</tr>
</tbody>
</table>

**Epinephrine**

- **Relative Potency of Ephedrine vs. Epinephrine = 65**

- **One study was cited that documented "beneficial" changes in hemodynamics among ventilated patients treated with i.e. epinephrine the day after major vascular surgery.

- **No citations comparing ephedrine to epinephrine provided for this estimate.**