# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205029Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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|---|---|
| **NDA #:** | 205029 |
| **Drug Name:** | Epinephrine Injection, USP 1:1000 (mg/mL) |
| **Indication(s):** | increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock |
| **Applicant:** | Belcher Pharmaceuticals, LLC |
| **Date(s):** | 11/30/2012 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | Division of Biometrics I |
| **Statistical Reviewer:** | Steve Bai, Ph.D. |
| **Concurring Reviewers:** | James Hung, Ph.D. Director DBI |
| **Medical Division:** | Division of Cardiovascular and Renal Products |
| **Clinical Team:** | Gail Moreschi, MD |
| **Project Manager:** | Russell Fortney |

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# 1 EXECUTIVE SUMMARY

Belcher did not conduct any clinical studies to assess the potential benefit of Epinephrine Injection USP, 1:1000 (1 mg/mL) in the aspects of the artial blood pressure. In-stead, Belcher relied on the established safety on the listed drug Twinject and the published literature. The clinical studies identified from the published literature seem to suggest that Epinephrine may have an effect to increase the arterial blood pressure, measured by MAP, in patients with septic shock. Although a large body of published literature is available, these studies do not rise to the level to be able to provide evidence for concluding the effectiveness of Epinephrine in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock.

# 2 INTRODUCTION

## 2.1 Overview

Belcher submitted this 505(b) (2) application for Epinephrine Injection USP, 1:1000 (1mg/mL). The proposed indication is for use in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock. This submission relies on published literature to support the efficacy of Epinephrine. Belcher is relying on safety information from Twinject (NDA 20800). Twinject is an approved Epinephrine (0.3 mg/mL) product for use in the emergency treatment of severe allergic reactions (Type I).

No clinical studies of Belcher's Epinephrine Injection USP, 1:1000 (1 mg/mL) have been conducted. The Agency agreed that a literature-only NDA submission was acceptable on an End of Phase I meeting held on 25 July, 2012. The published literature was searched for clinical studies of epinephrine used in the treatment of shock. A search of PubMed, using the terms epinephrine (adrenaline), hypotension, infusion, shock, sepsis, septic shock, human, patients, study, and/or clinical trial was performed. Searching all fields for "(septic shock)", "(blood pressure)", "infusion", "hypotension", and "(epinephrine or adrenaline)" led to 33 results. From these studies, articles relevant to epinephrine's use in hemodynamic support were reviewed, and 14 key articles (emphasizing randomized, controlled studies comparing intravenous epinephrine to alternative treatments) were selected to be summarized.

The Septic Shock (SS) in adults refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Septic shock is a severe form of sepsis with arterial hypotension despite adequate body fluid resuscitation (replacement). Furthermore, the sepsis is the clinical syndrome defined by the presence of both infection and a systemic inflammatory response (SIRS), and more specifically, SIRS in response to infection. The Septic shock accounts for about 9% of admissions to intensive care units, and its short-term mortality ranges between 40% and 60%.

Vasopressor is an intriguing hormone in that it has little vasoconstrictor effect in hemodynamically normal subjects, but is an important pressor in states where arterial pressure is threatened. It has been used in prevention and management of vasodilatory shock, as an alternative of catecholamine pressors. Intravenous Epinephrine has been used as a vasopressor

for over 50 years in treating hypotension associated with septic shock, as epinephrine significantly improves systemic arterial blood pressure. Intravenous infusions of epinephrine are well-defined both in published clinical studies and the algorithms of numerous medical organizations around the world, and are consistently recommended for the management of hemodynamic support.

### 2.2 Statistical Issues and Findings

The clinical efficacy data in this NDA come from published literatures. These studies were published and studied between the years of 1991 and 2007 within various countries. Therefore the data inherit biases such as publication bias, time lag bias, multiple publication bias, citation bias, language bias and outcome reporting bias.

In the clinical studies identified to support efficacy, none of them meets the standards of "adequate and well controlled study" for conducting a confirmatory trial. Statistical issues are found in all the studies, such as the endpoint of interest, MAP, was never defined in any studies, some studies did not have pre-defined primary endpoint, multiple endpoints yet without multiplicity adjustment, selectively reporting study result, and etc.

Therefore, the evidence for concluding the efficacy of Epinephrine in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock does not appear to be solid, because of the potential biases from published literature and the unresolved issues that hinder proper interpretation of the results of the studies. In this reviewer's opinion, the results from the identified studies and analyses are only exploratory.

### 2.3 Data Sources

There are no SAS datasets in this submission. The literature references and sponsor's summaries are stored in the directory of \\cdsesub1\EVSPROD\NDA205029 of the Center's electronic document room.

## 3 STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Literature Search Strategy

Currently, there are several unapproved and at least 39 approved drug formulations containing epinephrine currently marketed. Epinephrine injection is available in 1 mg/mL, (1:1000), 0.1 mg/mL (1:10,000), and 0.5 mg/mL (1:2,000) solutions. However, there is no FDA-approved intravenous epinephrine product for providing hemodynamic stabilization in septic shock patients. The only FDA-approved epinephrine products are intramuscular/ subcutaneous products (0.3 mg/delivery) for treating anaphylactic shock.



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Epinephrine for treatment of hypotension associated with septic shock has been assessed in over two dozen clinical studies published in the literature. The sponsor conducted a comprehensive literature search using PubMed and identified 14 key studies, which they believe can be used to demonstrate that epinephrine significantly improves systemic arterial blood pressure in hypotensive states associated with septic shock.

### 3.1.2 Clinical Efficacy Studies

The individual summaries of studies from the literature are divided by previous treatment and patient type. They are grouped by section as follows:

I. Patients with septic shock and no previous vasopressor treatment: 6 studies
II. Patients with septic shock and previous treatment with dopamine or dobutamine: 1 study
III. Patients with septic shock and failed response to dopamine: 4 studies
IV. Patients with septic shock, right ventricular failure, and failed response to dopamine and dobutamine : 1 study
V. Patients with septic shock or other conditions treated with epinephrine: 2 studies.

#### 3.1.2.1 Patients with septic shock and no previous vasopressor treatment

The sponsor had identified six studies, which recruited patients with septic shock and had no previous vasopressor treatment, see Table 1.

**Table 1 Tabular Summary of efficacy studies from published literature I**

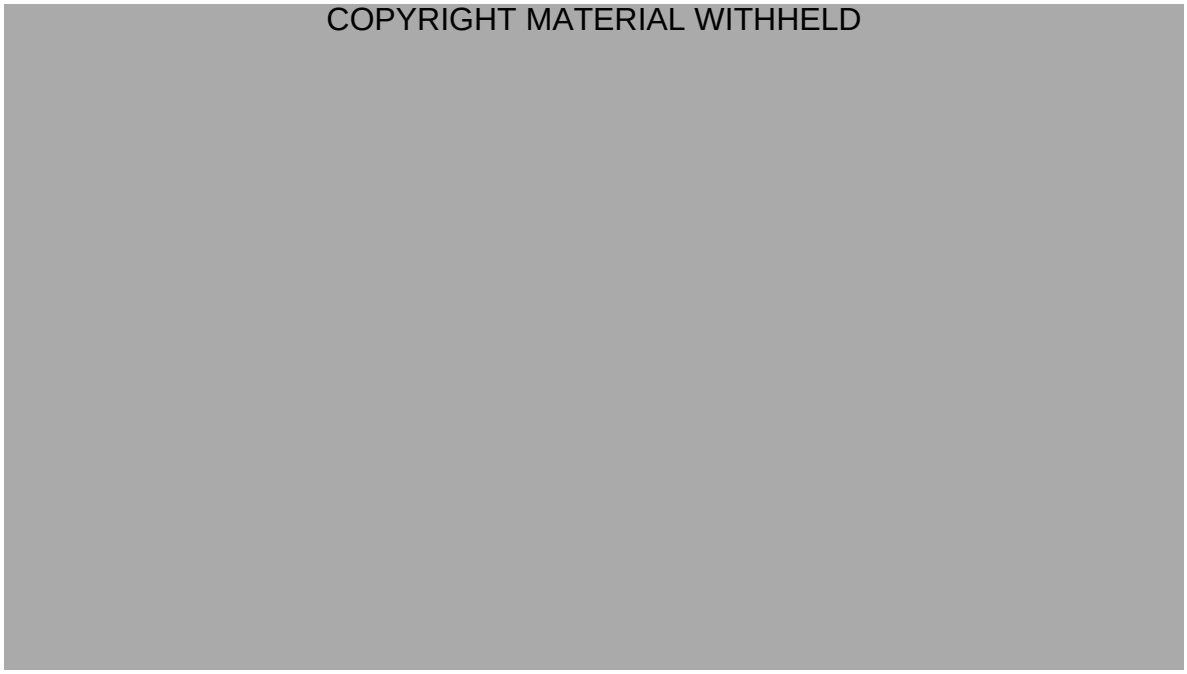
| Author, year | Objective | Study Design | Patient Population |
|---|---|---|---|
| Annane, 2007 | Compare norepi+dobutamine to epi in SS | Multicenter, DB, randomized, active-controlled clinical trial | 330 septic shock patients |
| Seguin, 2006 | Compare norepi+dopexamine to epi in SS to assess effects on gastric mucosal blood flow and on oxidative stress | Randomized, open-label trial | 22 septic shock patients |
| Seguin, 2002 | Compare norepi+dobutamine to epi in SS to assess effects on systemic and pulmonary hemodynamics, hepatic function, and blood gases. | Randomized, parallel group study | 22 septic shock patients |
| Moran, 1993 | To characterize the acute actions and physiologic dose profile of epi, as a single inotrope, in adult patients with SS | Prospective clinical study | 9 male and 9 female adult septic shock patients |
| Wilson, 1992 | To evaluate the effects of epi on Hemodynamics and oxygen transport when used as a first line inotropic agent in SS | Prospective study | 15 adult septic shock patients |
| Mackenzie, 1991 | To document the effects of epi on hemodynamics and oxygen transport in patients with SS persisting after fluid loading | Open-label Study | 13 adult septic shock patients |

[Source: Sponsor's Table 2.7.3.6.1 of Summary of Clinical Efficacy]

**Summary and conclusions:**

- Five of above six studies are small, open-label, or single armed trials. Annane (2007) was the only large randomized double blind clinical trial, which conducted in 330 adults to compare the efficacy and safety of norepinephrine plus dobutamine with those of epinephrine alone. The primary outcome was 28-day all-cause mortality. There are various secondary outcome endpoints and blood pressure measurements were taken from the patients. No type I error rate was controlled for the secondary endpoints. The primary finding of the study was that there was no significant difference between the two groups in mortality rates. Comparing epinephrine to norepinephrine plus dobutamine, there were 64 (40%) versus 58 (34%) deaths at day 28 ($p = 0.31$). Arterial hypotension is a main hemodynamic parameter of sepsis, so another finding of the study was on the blood pressure. The study claimed that the mean blood pressure increased to much the same extent in both groups after randomization, see Figure 1.

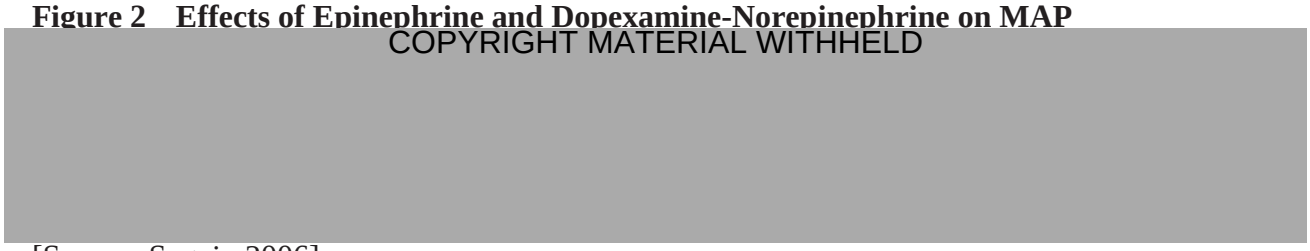
**Figure 1 Effects of treatment on mean blood atrial pressure**




[Source: Annane 2007]

- Seguin (2006) was an open-label, parallel-group, randomized study performed in a surgical intensive care unit among adults fulfilling usual criteria for septic shock. Systemic and pulmonary hemodynamics, GMBF (laser-Doppler) and malondialdehyde were assessed just before catecholamine infusion (T0), as soon as mean arterial pressure (MAP) reached 70 to 80 mmHg (T1), and 2 hours (T2) and 6 hours (T3) after T1. There was no significant difference between groups for MAP at T0, T1, T2, and T3.

**Figure 2 Effects of Epinephrine and Dopexamine-Norepinephrine on MAP**




[Source: Seguin 2006]

Epinephrine and dopexamine-norepinephrine both increased MAP in a similar extent when compared to baseline. It also appeared that blood pressures had been stabilized after T1 in both groups, see Figure 2.

- Seguin (2002) was a parallel group study comparing epinephrine (N = 11) with the combination of dobutamine and norepinephrine (N = 11) on gastric perfusion in patients with septic shock. At baseline, MAP was 54 ± 8 mmHg in the epinephrine and 51 ± 8 mmHg in the dobutamine-norepinephrine group, and at time of evaluation, MAP was 78 ± 3 mmHg in the epinephrine and 77 ± 5 mmHg in the dobutamine-norepinephrine group. Note, Seguin (2002) never stated when the time of evaluation is.

- Moran (1993) was a prospective clinical study conducted to characterize the acute actions and physiologic dose profile of epinephrine as a single inotrope in 9 male and 9 female adult patients with septic shock. In the dose range of 3 to 18 μg/min, epinephrine produced linear increases in MAP, see Figure 3.

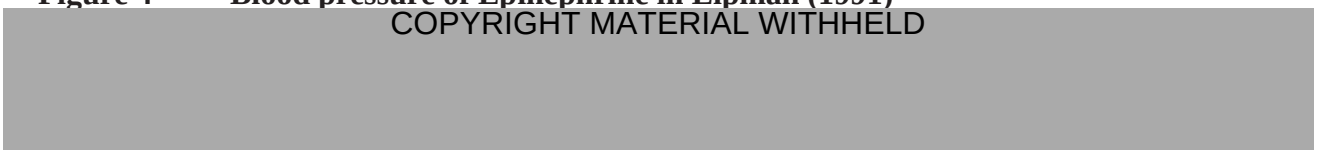
**Figure 3 Hemodynamic data during epinephrine infusions**


[Source: Moran (1993)]

### 3.1.2.2 Patients with septic shock and previous treatment with dopamine or dobutamine

Lipman (1991) was an open-label, single-group study in 10 patients with 11 episodes of septic shock to assess the hemodynamic effects of epinephrine in septic shock. The study showed that epinephrine increased MAP from baseline, see Figure 4.

**Figure 4 Blood pressure of Epinephrine in Lipman (1991)**

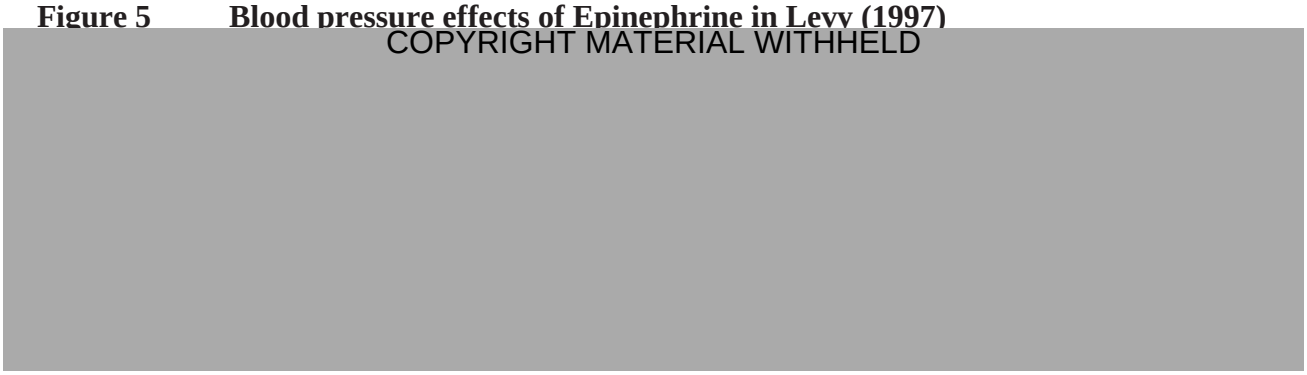



[Source: Lipman (1991)]

#### 3.1.2.3 Patients with septic shock and failed response to dopamine

In these patients, Levy (1997) showed that epinephrine increased MAP when compared to baseline to a similar extent as norepinephrine with or without dobutamine, see Figure 5. The study enrolled 30 septic shock patients. The measurements were repeated 1, 6, 12 and 24 hours post baseline.

**Figure 5 Blood pressure effects of Epinephrine in Levy (1997)**




[Source: Levy (1997)]

#### 3.1.2.4 Patients with septic shock, right ventricular failure, and failed response to dopamine and dobutamine

Le Tulzo (1997) was a descriptive study with 14 septic shock patients, which showed the MAP increased to 74 mmHg within 2 hours after Epinephrine was started. The baseline MAP was 58 mmHg.

#### 3.1.2.5 Patients with septic shock or other conditions treated with epinephrine

Myburgh (2008) compared MAP between epinephrine (N=76) and norepinephrine (N=82), and claimed that epinephrine increased MAP compared to baseline to a similar extent as norepinephrine.

### 3.2 Reviewer's Conclusion

Belcher did not conduct any clinical studies for Epinephrine Injection USP, 1:1000 (1 mg/mL). This NDA is a literature-based submission, which presented the summaries of efficacy results and key design elements of published articles found during searches of the literature. The reviewer had examined and provided the snapshots of the 14 key reference studies in the

previous sections. The findings on potential benefit on MAP were based on it being post-hoc endpoint and post-hoc analysis in above studies. These were driven by post-hoc explorations. Thus, these studies are exploratory to generate some interesting hypotheses.

The applicant attempted to argue that in studies including patients with septic shock that assessed MAP in comparison to pretreatment values, epinephrine was shown to have effects on MAP. The reviewer has the following observations based on 4 double-blinded, active controlled studies:

- Annane (2007) is the only large double-blinded, randomized active-controlled clinical trial. The study did not list MAP as one of the efficacy endpoints, Figure 1 showed blood pressure quickly increased just after 2 days of treatment in both treatment groups and appeared to maintain the blood pressure goal of 70 to 80 mmHg throughout the remainder of the trial.

- Seguin (2002) compared various systemic and pulmonary hemodynamic values between 11 Epinephrine and 11 dobutamine-norepinephrine patients. As the review had stated in the Section 3.2.2.1, that both groups raised MAP effectively at the time of evaluation. There was no significant difference between groups regardless of the systemic and pulmonary hemodynamic or blood gas variable considered.

- Levy (1997) was a prospective, randomized clinical trial to compare the effects of norepinephrine and dobutamine (N = 15) to epinephrine (N = 15) on hemodynamics, lactate metabolism, and gastric tonometric variables. No statistical difference was found between epinephrine and norepinephrine-dobutamine for systemic hemodynamic measurements. These measurements were repeated after 1, 6, 12, and 24 hours. As we can see from Table 2, epinephrine increased MAP from the baseline in both treatment groups.

**Table 2 Effects of MAP on epinephrine and norepinephrine-dobutamine, Levy(1997)**

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[Source: Levy (1997)]

- Myburgh (2008) was another large multicenter, double-blind, randomized, controlled trial conducted to determine whether there was a difference between epinephrine (N = 139 [76 had septic shock]) and norepinephrine (Levophed; N = 138 [82 had septic shock]) in achieving MAP goal in a heterogeneous population of ICU patients requiring vasopressors for any cause at randomization. Patients with septic shock (N = 158; septic patients who required study drug were considered to have septic shock) and acute circulatory failure (N = 128) were analyzed separately. Primary outcome was achievement of MAP goal for more than 24 hours without vasopressors. Secondary outcomes were 28 and 90-day mortality.

**Figure 6 Comparisons between epinephrine and norepinephrine on MAP in Myburgh**


[Source: Myburgh (2008)]

The sponsor attempted to use Figure 6 suggest that the epinephrine increased MAP compared to baseline to a similar extent as norepinephrine. However, there are two curves with opposite trend in the figure, solid and hollow bullets. The paper never explained which curve is MAP.

The identified four active controlled studies seem to suggest that Epinephrine may have an effect on improving arterial blood pressure in patients with septic shock. However, these clinical efficacy data came from published literatures. These data potentially inherited number of biases such as publication bias, time lag bias, multiple publication bias, citation bias, and outcome reporting bias. Furthermore, none of them met the standards of "adequate and well controlled confirmatory trial." None of them provided the endpoint of interest, MAP, as the efficacy endpoint and some studies have multiple endpoints yet without multiplicity adjustment. There is another common statistical issue with all the active controlled studies. These studies are all designed as superiority studies, but all of them attempted to show the equivalence between the treatment arms in the specified primary efficacy endpoint, respectively. Therefore, based on these statistical issues, these studies do not provide conclusive evidence for the effectiveness of Epinephrine in terms of raising blood pressure. However, they may provide some possible signals on these benefits.

## 4 CONCLUSIONS AND RECOMMENDATIONS

Belcher did not conduct any clinical studies to assess the potential benefit of Epinephrine Injection USP, 1:1000 (1 mg/mL) in the aspects of the artial blood pressure. In-stead, Belcher relied on the established safety on the listed drug Twinject and the published literature. The clinical studies identified from the published literature seem to suggest that Epinephrine may have an effect to increase the arterial blood pressure, measured by MAP, in patients with septic shock. Although a large body of published literature is available, these studies do not rise to the level to be able to provide evidence for concluding the effectiveness of Epinephrine in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock.

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/s/

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STEVE G BAI
09/09/2013

HSIEN MING J HUNG
09/09/2013

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 205029** **Applicant: Belcher Pharmaceuticals, Stamp Date: 12/4/2012**

**Drug Name:** (b) (4) **NDA/BLA Type: NDA literature based 505(b)(2)**

On **initial** overview of the NDA/BLA application for RTF:

| | Content Parameter | Yes | No | NA | Comments |
|---|---|---|---|---|---|
| 1 | Index is sufficient to locate necessary reports, tables, data, etc. | | | X | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | | | X | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable). | | | X | |
| 4 | Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets). | | | X | |

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|---|---|---|---|---|
| Designs utilized are appropriate for the indications requested. | | | X | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | | | X | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | | | X | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | | | X | |

File name: 5_Statistics Filing Checklist for a New NDA 205029

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

| | |
|---|---|
| Steve Bai | 1/23/2013 |
| Reviewing Statistician | Date |
| James Hung | 1/23/2013 |
| Supervisor/Team Leader | Date |

File name: 5_Statistics Filing Checklist for a New NDA 205029

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STEVE G BAI
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