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Invited Commentary

Xuebijing Injection for the Treatment of Sepsis
What Would a Path to FDA Approval Look Like?

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Sepsis is a serious condition with high morbidity and mortality for which treatment advancements are desperately needed. In this issue of *JAMA Internal Medicine*, Liu et al[1] describe the results of Efficacy of Xuebijing Injection in Patients With Sepsis (EXIT-SEP), a large, multicenter, single-country, double-blind, placebo-controlled randomized clinical trial of Xuebijing injection (XBJ), an intravenous herbal preparation, for the treatment of sepsis. With more than 900 patients in each treatment group, 28-day all-cause mortality was 18.8% in the XBJ group and 26.1% in the placebo group, for an absolute risk difference of 7.3 (95% CI, 3.4-11.2) percentage points ($P < .001$). These results are certainly intriguing; one might wonder how an herbal preparation such as XBJ might gain US marketing approval. Major issues include (1) XBJ is an herbal preparation and not a drug; (2) there is only a single efficacy study; and (3) the EXIT-SEP trial was conducted entirely outside the US, in 1 country (China).

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The US Food and Drug Administration (FDA) regulates an herbal product as a drug if it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease.[2] Thus, a botanical product such as XBJ would be held to the same approval standards as a drug. Prior to approval, the FDA must determine that (1) the drug is safe and effective for its proposed use and that its benefits outweigh its risks; (2) the la-

beling contains the information necessary to use the drug appropriately; and (3) the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to ensure the drug's identity, strength, quality, and purity. Moreover, there are additional considerations for herbal preparations because of their unique nature and inherent complexities.

Prior to approval, a drug's effectiveness much be established through the generation of "substantial evidence of effectiveness." This legal standard is typically met through 2 independent, adequate and well-controlled trials, each convincing on its own. Substantiation of the results of the first study with a second study is intended to decrease the possibility that positive results are due to chance. Under certain circumstances, however, a single trial may satisfy the legal requirement for substantial evidence of effectiveness. Typically, a single trial would be large and enroll a diverse range of participants across a large number of study sites, with demonstration of a clinically meaningful and statistically very persuasive effect on mortality or severe or irreversible morbidity. No single site should drive the treatment effect by virtue of its effect size or its particularly large number of patients. The demonstration of consistent and clinically meaningful effects on distinctly different, yet mutually supportive, prospectively planned end points can also lend support to a single-trial approval. Generally, in this scenario, there would not be equipoise for conducting a confirmatory trial.

Could the EXIT-SEP trial[1] provide substantial evidence of effectiveness as a single trial? This was certainly a large trial with multiple centers (45), and the results demonstrate a clinically meaningful and statistically persuasive effect on mortality; however, other characteristics noted above are absent or uncertain. It would be difficult to conclude that the study enrolled a broad range of participants. The secondary end points were only exploratory in nature, as there was no control of the type I error rates. Moreover, none of the secondary end points were intended to demonstrate an effect on a separate aspect of sepsis or support a specific mechanism of action of XBJ. There is no information in the article regarding the possibility that a single large site drove the overall results.

The FDA has the legal authority to accept foreign data as the sole basis for a marketing approval if the data are deemed applicable to the US population and relevant to US medical practice. The authors[1] note the limited generalizability of their findings and state that the mortality rate from sepsis in China differs from other countries based on information from previous sepsis trials. Thus, questions could be raised regarding genetic differences that might affect treatment responses, as well as differences in the practice of medicine in China. The primary infection sites in the EXIT-SEP study seem unusual for a US sepsis population, with high rates of lung (45%) and intra-abdominal infections (32%).

The study[1] did not appear to enroll many patients with severe sepsis. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was approximately 12 in both groups, and only 3.5% of patients had baseline APACHE II scores of 25 or greater (the APACHE II score is a disease severity classification with a 0 to 71 range; higher scores indicate worse disease severity). At baseline, mean systolic and diastolic blood pressures were 119 and 69 mm Hg, respectively. The article does not report the numbers of patients aged 65 years and older. Patients older than 75 years were excluded.

In a study of hospitalized patients only 28 days in duration, missing vital status should be rare (≪1%). In this trial,[1] vital status was unknown for 33 patients (3.6%) in the XBJ group and 24 patients (2.6%) in the placebo group. Missing efficacy data can undercut the persuasiveness of a trial, especially if there is a difference between treatment groups, as was the case here.

The adverse event rates were extremely low compared with the rates that would be expected in the US. The study protocol[1] explains that "events that are part of the natural history of the primary disease process or expected complications of critical illness will not be reported as SAEs [serious adverse events]." Thus, the threshold for reporting serious adverse events was quite high. The article provides reassurance that there were no drug-related serious adverse events in the study. Obviously, numerous serious adverse events occurred during the study, as approximately 22% of the patients died. Thus, it seems clear that the investigators deemed all serious adverse events to be disease-related, and none to be drug-related. In fact, causality determinations are difficult for investigators and often biased. The safety of XBJ would be difficult to characterize, therefore, based on these adverse event data. Although the mortality benefit would likely outweigh any safety concerns identified, it is nevertheless important to characterize the risks of a drug to write adequate instructions for use.

The FDA issued a guidance document to assist sponsors in developing the quantity and quantity of information needed to support approval of a botanical drug product.[3] The guidance recognizes that as a heterogeneous mixture, the chemical constituents of a botanical drug may not be well defined or even, in some cases, identified. These characteristics have implications for the manufacturing process and for product characterization. Evidence must be provided that the product tested in the clinic matches the marketed product, and that the marketed product can be manufactured or produced consistently. Establishing the identity and purity of a botanical drug relies on chemical characterization of molecules in the mixture, as well as agricultural and processing aspects unique to botanicals (eg, seasonal growing conditions, growing sites).

Finally, to gain US marketing authorization for a new drug, a new drug application (NDA) must be submitted by an applicant. This individual or entity owns the NDA, takes responsibility for its content, and provides the data (or access to the data) and supplementary information. For submission of an NDA where clinical data are required, the current application fee is approximately $3.2 million. New drug applications for certain rare diseases are exempt from application fees.[4]

In summary, the results of EXIT-SEP[1] are promising but have important limitations. An international trial that enrolls a diverse patient population with a range of base-

line sepsis severities that provides excellent patient retention and ascertainment of vital status would be desirable to confirm these findings and ensure generalizability. Finally, the FDA holds botanical drug products to the same approval standards as any drug. Unique manufacturing issues should be addressed throughout development.

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