GlobalData
OpportunityAnalyzer

SEPSIS —
OPPORTUNITY ANALYSIS AND FORECASTS TO 2021
**Executive Summary**

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Table above presents the key metrics for sepsis products in the six major pharmaceutical markets (6MM), which include the US and 5EU (France, Germany, Italy, Spain, and the UK).

After the Launch of the First Sepsis-Specific Product in 2016, the Market is Projected to Experience Modest Growth Through 2021

For the purposes of this report, GlobalData defines the sepsis market to include sales of sepsis-specific, host-directed products across the 6MM. Therefore, detailed analyses and sales projections for products not specifically indicated for sepsis patients, such as currently licensed antibiotics, are beyond the scope of this report. In 2016, GlobalData projects the sepsis market to be valued at $25.7m across the 6MM. The US is expected to account for almost 80% of the 2016 market share, with sales of $20.3m. In the 5EU, 2016 sales are expected to reach $5.4m (a little over 20% of market share).

Over the course of the 2016–2021 forecast period, GlobalData expects sales to increase modestly and reach a combined $354.0m in 2021 in the 6MM, at a Compound Annual Growth Rate (CAGR) of 69.0%. GlobalData believes that this growth will be driven by the increased uptake of novel therapies — led by Asahi Kasei Pharma America’s (AKP-A’s) anti-coagulant ART-123 (recombinant human soluble thrombomodulin alpha) — in select patients as the critical care community regains confidence in sepsis-specific products and as more data is generated on their overall efficacy and safety. Despite this projected growth, developers looking to enter the sepsis market must be aware of skepticism towards sepsis products, which emerged after the
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worldwide voluntary recall of Eli Lilly’s anticoagulant Xigris (drotrecogin alpha [activated]) in 2011, the last product to be approved and marketed for sepsis. Sales growth will likely be hindered by this guarded climate throughout the duration of the forecast period.

Given its status as the most advanced pipeline candidate, GlobalData anticipates that AKP-A’s ART-123 will dominate the market, with 2021 sales projected to reach $190.2m and $55.1m across the US and 5EU, respectively. GlobalData expects the earlier-stage pipeline products to garner a little more than 30% of market share by 2021, primarily because they will not reach the market until the end of the forecast period. However, primary and secondary research indicated that these early-stage approaches, particularly immunomodulatory agents, offer the most promise because their major mechanisms of action (MOAs) are directed at the irregular immune response that is causing the sepsis syndrome.

GlobalData expects several major factors to drive growth in the sepsis market across the 6MM:

- Companies competing to develop novel sepsis therapies will becoming increasingly open to exploring innovative research and development (R&D) strategies centered on clinical trial design during the forecast period. These firms will attempt to leverage interim analyses, biomarkers, and companion diagnostics to improve patient targeting. The anticipated use of endpoints other than 28-day all-cause mortality will also allow drug developers to better position their products as effective options for select patient populations, thereby overcoming patient heterogeneity challenges.
- An increased emphasis on the education of healthcare providers, aided by streamlined clinical practice guidelines and an improved understanding of sepsis pathophysiology, is expected to help hasten the uptake of novel therapies indicated for the narrow segments of the sepsis population that do not respond to currently available basic supportive care options.
- The launch of several sepsis-specific products will foster more development and innovation in the space because companies will see that it is possible to successfully navigate clinical development with a sepsis-specific product.
GlobalData believes several notable barriers will affect growth in the sepsis products market across the 6MM:

- The formidable scientific challenges associated with patient enrollment and endpoint selection during clinical trials will still remain, as biomarkers and companion diagnostics have not caught up to the products within the pipeline. A shift in the trial design paradigm must occur for novel interventions to have a sustained positive impact in actual clinical settings.

- The heterogeneity of the presenting patient population and the lack of a universally accepted, specific, and streamlined set of diagnostic criteria to stratify patients will make patient targeting for clinical trials difficult. An incomplete understanding of sepsis pathophysiology, while expected to improve during the forecast period, will still exacerbate these challenges.

- Inadequate awareness, both on the part of the public and healthcare providers, will likely hinder the uptake of novel therapeutics throughout the forecast period. Firms can potentially circumvent this obstacle by becoming actively involved in efforts to improve the level of sepsis awareness and education. This is particularly important in the post-Xigris marketplace, as firms will benefit from a proactive and hands-on approach with their new products.

- A climate of healthy skepticism and guarded optimism regarding the clinical relevance and cost-effectiveness of sepsis-specific therapies, which stems from the withdrawal of Xigris and high-profile discontinuations of late-stage pipeline products, is expected to slow uptake of novel drugs for the duration of the forecast period.

Figure below illustrates the expected sales for sepsis products in the 6MM at the beginning and conclusion of the forecast period.

Source: GlobalData, based on primary research interviews with sepsis specialists

5EU = France, Germany, Italy, Spain, and UK
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Developers Must Leverage Innovative R&D Strategies to Target Appropriate Patients and Achieve Sustained Commercial Success

Despite a high level of unmet need in the sepsis marketplace, licensure will not ensure rapid uptake of sepsis-specific agents. This uncertainty is directly related to clinicians’ skepticism surrounding the validity of clinical studies assessing the safety and efficacy of investigational therapies across a pool of patients with high heterogeneity. This cautious stance towards sepsis pipeline products has only been exacerbated as drug developers in the last several years routinely failed to show a survival benefit or to demonstrate the clinical relevance of alternative endpoints that should be strongly considered by regulators for approval.

In order to combat these market realities, GlobalData believes developers will have to leverage innovative R&D strategies to establish the strong clinical evidence needed for approval and uptake post-licensure. Some of the key approaches identified by KOLs include adaptive clinical trial design, including interim analyses leveraging multiple clinically relevant biomarkers, and companion diagnostics to limit heterogeneity among enrolled patients; targeting highly specific sepsis patient populations based on sepsis-induced conditions; and investigating novel targets with combination therapies that are relevant to sepsis pathophysiology. Specifically, primary research indicated that physicians were most excited about targeting sepsis patients who have become immunosuppressed and treating them with immunostimulatory compounds.

High Unmet Need for Safe and Efficacious Products Will Exist Throughout the Forecast Period

GlobalData classifies the overall level of unmet need in the sepsis market as high. KOLs from across the 6MM have cited the absence of a licensed sepsis-specific product as the greatest unmet need across the marketplace, agreeing that clinicians would welcome the addition of novel therapies that target the underlying causes of sepsis to their treatment arsenal. Interviewed experts also stressed that improving the medical community’s understanding of sepsis pathophysiology will lead to the discovery of more clinically relevant targets and leads, along with novel biomarkers and companion diagnostics that will aid in drug development. GlobalData expects there will be ample opportunity for companies to exploit these unmet needs throughout the forecast period.

GlobalData’s primary research revealed that improved sepsis public awareness campaigns and physician education will help to decrease mortality, primarily due to early recognition and delivery of the current basic treatment options (adequate antibiotics and fluid resuscitation). However, GlobalData believes there is still room to develop products to be delivered to the patients who do not respond to these basic and non-specific initial treatment options.
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Opportunities Remain for Current and Future Players to Develop Therapies Targeting Sepsis-specific Pathophysiology

With the current treatment options for sepsis comprising well-established interventions such as antibiotics, fluid resuscitation, and organ-specific support, experts revealed to GlobalData that developers should focus their efforts on developing innovative immunomodulatory agents that target sepsis-specific pathophysiology. KOLs were particularly excited about the potential of immunostimulatory agents and their ability to treat the subpopulation of patients with sepsis-induced immunosuppression, but also cited the opportunity to develop agents that correct for the imbalanced inflammatory response that is characteristic to all sepsis patients. Opportunities will also exist for firms developing novel therapies that target comorbid conditions, with products currently in development targeting sepsis patients with disseminated intravascular coagulopathy (DIC), ALI, and acute kidney injury (AKI) as examples of this approach. GlobalData ultimately views innovative clinical trial design, companion diagnostics, and proper patient targeting to limit heterogeneity as crucial for the successful licensure of developmental products, particularly those aimed at modulating a patient’s immune response.

The Sepsis Pipeline, Which Includes the Anticoagulants ART-123 and ALT-836, Offers a Glimmer of Hope, but Further Improvements are Necessary

The collective opinion among KOLs interviewed by GlobalData regarding the clinical-stage sepsis product pipeline was one of cautious optimism. The critical care community is not overly confident that these investigational agents will prove to be clinically beneficial in their selected trial participants, but they will welcome any of their approvals if they display convincing results. Many experts view the experimental products as having the potential to improve clinical outcomes for patients, but they stressed that the drug makers’ clinical trial design approaches are similar to those of recent failures. For example, KOLs agreed that AKP-A’s pivotal Phase III trial for ART-123 should target a narrower patient population in order to maximize the chance of meeting their efficacy endpoints. While these concerns will slow its uptake, GlobalData still expects ART-123 garner sales of $245.3m in the 6MM by 2021.

Experts were also intrigued by Spectral Diagnostic’s hemofiltration device Toraymyxin and its ability to remove endotoxin from the blood, because the company leveraged an endotoxin activity assay (EAA) companion diagnostic to identify patients who are most likely to benefit from its use. While a detailed projection of annual sales for the Toraymyxin device is beyond the scope of this report, its uptake in the US and 5EU will likely
be predicated on Spectral’s ability to demonstrate efficacy in this specific patient population.

KOLs are eagerly awaiting further data in human trials for early-stage products, and they expressed hope that companies developing these products will improve clinical trial design and use proper patient targeting. Such pipeline agents, projected to launch later in the forecast period, are led by Altor Bioscience’s anticoagulant ALT-836 (recombinant chimeric anti-tissue factor antibody). AM-Pharma, with its lead sepsis product, recAP (recombinant human alkaline phosphatase), has been praised by KOLs as one of the first companies to leverage innovative adaptive trial design. Products such as Leading BioSciences’ LB-1148 (tranexamic acid) and InflaRx’s IFX-1 (humanized anti-complement monoclonal antibody) were also cited as having intriguing MOAs that warranted further investigation for use in sepsis patients, and Ferring Pharmaceuticals’ selepressin offers promise as a vasopressor with reduced off-target effects. GlobalData believes there will be ample opportunity for developers to enter clinical development with more clinically relevant and novel drug targets whose approach is better directed to the relevant patient population throughout the forecast period.

Figure below summarizes the competitive assessment of the most promising sepsis pipeline candidates in clinical development from 2016–2021. GlobalData based the ratings for each pipeline agent’s clinical and commercial attributes on discussions with KOLs from across the markets covered in this report, analysis of clinical trial data, and a thorough review of the literature.

![Competitive Assessment of Sepsis Pipeline Products, 2016–2021](image-url)

Source: GlobalData, based on primary research interviews with sepsis specialists

*The projection of annual sales ($) for devices is beyond the scope of this report. However, anticipated launch dates and patient uptake estimates for devices GlobalData expects to be indicated for sepsis patients are included in the forecast model.
Executive Summary

What Do Physicians Think?

The KOLs interviewed for this report shared their expert insight on the sepsis products marketplace. The consensus among experts was that they were not extremely excited about the current clinical-stage pipeline, and there is plenty of opportunity for improvement. Physicians noted that the majority of late-stage investigational products do not target the underlying cause of sepsis, which is the patient's improper and imbalanced immune response to infection. Furthermore, many experts cited clinical trials as being designed too similarly to those of recent product withdrawals and discontinuations. The high-profile failures of the recent past, which have reduced the number of players and increased uncertainty surrounding current investigational products, have also contributed to a guarded outlook on the pipeline by KOLs.

“[As for the pipeline as a whole], I’m not as excited as I was in the past because there’s not as many players involved. The two leading therapies [in clinical-stage development], ART-123 and Toraymyxin, I’m somewhat skeptical of them. I don’t think those are the closest to the market… It’s hard to be that excited. You can tell I’m not that excited.”

US Key Opinion Leader

“I hope [treatments for sepsis progress in a positive direction]. But it's very, very difficult to say right now.”

EU Key Opinion Leader

“Clearly [there are not] as many [investigational products] as [there] used to be in the pipeline, but that’s because there’s such cynicism and skepticism now due to all the failures of the past.”

US Key Opinion Leader

Despite their largely unenthusiastic view of the pipeline, KOLs believed that, in the next five years, more pipeline products will be aimed at targeting the immune pathophysiology of sepsis, an approach they see as being essential to improving clinical outcomes for many sepsis patients. More specifically, they thought firms should be developing companion diagnostics to pair with products that alter the immune system in order to better identify patients most likely to benefit from the specific intervention. Furthermore, rapid point-of-care diagnostics for early recognition of infection and accurate pathogen identification were also seen as highly important.

“In the next five years, I can see sepsis product development trying to improve early recognition of sepsis and its underlying causative pathogen. I can also see treatments that are specific to the evolution of the inflammatory process. Specifically, products that are able to determine the pro- or the anti-inflammatory status of the patient so interventions can be directed to turn the inflammation up or down, whichever is needed.”

EU Key Opinion Leader
“It’s not about knowing how fast [immune mediators] change. It’s about knowing what we would do with the information. If you told me that [you had a test] and it gave a read out of the overall activity of immune cell function in the circulation — even though the circulation is only one window in the body — and you said this test tells you what this looks like every six hours and you need to measure it every six hours because it goes up and down. If it’s going up and down all over the place, tell me the drug that I am going to use to treat the patient. I have no drug that titrates its response for immune-boosting activity up and down by the hour. Again, these things are interesting to think about, but they almost need to be coupled to a therapeutic development at the same time.”

US Key Opinion Leader

“But even if we look at something as simple as giving a right antibiotic to a patient on time, in our emergency departments, which are relatively well resourced for patients with severe sepsis and septic shock, only 30% of patients are getting their antibiotics on time. Again, until we fix these basic aspects of care, any interventional therapeutic aspects become less relevant.”

EU Key Opinion Leader

“KOLs agreed that clinical trial design and patient targeting are the most critical aspects to developmental success of current sepsis pipeline products. Experts believed that developers must learn from the mistakes of their predecessors by recognizing the important role patient heterogeneity will play in clinical trial design, most heavily influencing enrollment criteria and endpoint selection.”

EU Key Opinion Leader

“If anything’s going to be available on the market in the next five years it’s going be an immunostimulatory molecule.”

US Key Opinion Leader

“The early recognition [of specific pathogens is important]. Currently, we rely on microbiology and blood cultures to identify the presence of bacteria, and this takes at least 24 hours. I think the perspective is to have early identification of the bug and therefore early optimal treatment with the antibiotics. We have some products that may allow this. But I think there are issues of cost and issues with sensitivity and specificity.”

EU Key Opinion Leader

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“When drugs are further along in clinical development the trend needs to be having quantitative inclusion and exclusion criteria to really look at a specific patient population. I consult for a lot of different companies and they still want to start off with the big population. It takes some convincing because their hope from their marketing end is to achieve the largest patient population possible. That doesn’t mesh with who they’re likely to benefit. The hope in the future is that these novel therapeutics will actually target the population that would benefit from them.”

US Key Opinion Leader

“A one-size-fits-all blockbuster drug is not going to happen because of the heterogeneity of the patients, the lack of the exclusion of the patients who are going to do well with standard background care, and the lack of focus on the population with the clinical phenotype most likely to benefit from the particular drug’s mechanism of action.”

US Key Opinion Leader

“In the next five years I see the treatment of sepsis patients becoming more targeted at specific patient populations. Looking at both phases — the inflammatory and the anti-inflammatory — and trying to identify the right patients. For instance, one patient may actually need an up-regulation of the inflammatory response, and conversely the other would need a down-regulation of the inflammatory response.”

EU Key Opinion Leader

“That’s been the story in a lot of sepsis drugs. There are a lot of [agents] out there that probably should have been positive. [Their trials] were just designed wrong. The way you design the trial all depends on how you think the drug works... you want to pick up the patients who are at risk and you don’t want to go into a whole bunch of countries where the background care is suspect.”

US Key Opinion Leader

“We historically have on the shelf really quite a large number of therapeutic trials with equivocal results, and to my mind the main issue with that is that we’re putting a very heterogeneous cohort of patients into one pot, naively assuming that we can treat them all the same. They’re heterogeneous, of course, in the origin of their disease, but more importantly for me in terms of the stage of progression of their disease. We are not working in the public sector to try and get patients to the hospital quickly, we’re not working on how we can identify sepsis in its early stages, and only until we’ve done that, until we’ve reduced the heterogeneity of the disease, then we’re going to continue to see equivocal therapeutic trials.”

EU Key Opinion Leader
Executive Summary

“If you were starting tomorrow with a platform in [the sepsis space], I would propose doing a learning enrichment design, where you have some putative biomarkers that may work but you don’t bet the farm on it. As the trial goes along, if it turns out that you were right after all and the drug works best in patients who are biomarker-positive for this particular test, then [you would] only enroll those patients in the second half of the trial. But the last thing you’d want to do is do the whole trial, and then afterwards think, “That wasn’t a good biomarker after all.” That would just waste a lot of money and kill the drug.”

US Key Opinion Leader
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Introduction

2 Introduction

2.1 Catalyst

Sepsis has quietly evolved into one of the most urgent medical issues facing healthcare systems in the US and 5EU (France, Germany, Italy, Spain, and the UK) today. According to the Centers for Disease Control and Prevention (CDC), sepsis rates doubled between 2000 and 2008, and sepsis was the 11th leading cause of death in the US in 2010 and the single most expensive condition treated in US hospitals in 2011. Severe sepsis cases involving multiple organ dysfunctions are associated with especially high morbidity and mortality, and consume a vast amount of healthcare resources. Furthermore, key opinion leaders (KOLs) indicated to GlobalData that many survivors experience difficulties in becoming productive members of society again.

Given the clear need for novel sepsis-specific interventions, the global sepsis marketplace — which, for the purposes of this report, consists of the US and 5EU — should represent an untapped commercial opportunity for drug developers. The current sepsis pipeline, however, features no drug candidates in late-stage clinical development by the large pharmaceutical companies. The discontinuation of Eli Lilly's once-marketed sepsis drug Xigris (drotrecogin alfa [activated]), a recombinant human activated protein C, left no sepsis-specific host-directed product available for physician use. Its exit from the market left significant unmet medical need and has been followed by a parade of late-stage failures such as Eisai's Eritoran (eritoran tetrasodium), AstraZeneca and BTG's CytoFab (formerly AZD-9773), and Agennix's talactoferrin alfa (recombinant human talactoferrin). These failures, however, highlight the need for a paradigm shift in how late-stage sepsis clinical studies are conducted. More specifically, GlobalData anticipates that drug developers must explore alternative approaches to patient recruitment and endpoint selection in order to streamline product development and ensure the correct patients are receiving their investigational interventions.

GlobalData expects the following key factors will contribute to the evolution of the sepsis marketplace during the forecast period from 2016–2021:

- The arrival of novel pipeline agents indicated for niche patient populations, led by ART-123, will drive growth in the global sepsis marketplace from 2016–2021 and renew development and innovation in the space, because companies will see that it is possible to successfully navigate clinical development with a sepsis-specific product.
Introduction

- Companies competing to develop novel sepsis therapies during the forecast period will begin to rely more heavily on innovative research and development (R&D) strategies centered on clinical trial design. These firms will attempt to leverage interim analyses, biomarkers, and companion diagnostics to improve patient targeting. The anticipated use of alternative endpoints other than 28-day all-cause mortality will also allow drug developers to better position their products as effective options for select patient populations, thereby overcoming patient heterogeneity challenges.

- Despite healthy progress in trial design, a climate of healthy skepticism and guarded optimism regarding the clinical relevance and cost-effectiveness of sepsis-specific therapies, which stems from the withdrawal of Xigris and high-profile discontinuations of late-stage pipeline products, is expected to slow uptake of novel drugs during the forecast period.

2.2 Related Reports

Introduction

2.3 Upcoming Related Reports

Appendix

10.7 About GlobalData

GlobalData is a leading global provider of business intelligence in the Healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports and forecasts. Our analysis is supported by a 24/7 client support and analyst team.

GlobalData has offices in New York, Boston, San Francisco, London, India and Singapore.

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