Increase In Antibacterial R&D Prompts EMA Proposal For Improved Guidance

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Executive Summary

Following a resurgence of activity in the field of antibacterial products, the European Medicines Agency has proposed merging and updating its two existing guidelines on this topic into a single, clearer, core document.

THE EMA'S NEW ANTIBACTERIALS GUIDANCE WILL BE A SINGLE CORE REFERENCE DOCUMENT

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The European Medicines is proposing to update its two existing guidelines on the clinical evaluation of medicines for treating bacterial infections and merge them into a single core document. The new document would clarify, among other things, considerations for the acceptance of single pivotal studies to support infection-site specific indications and pathogen-specific indications.

A draft version of the new guideline is expected to be issued for stakeholder consultation by the fourth quarter of this year. When finalized, it will replace and revise the EMA's "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 2)," which was adopted in 2011 and came into force in 2012, and a related addendum (EMA/CHMP/351889/2013), which was adopted in 2013 and came into force in 2014.

Better Flexibility And Focus

The EMA's proposal – outlined in a draft concept paper - appears to show a move towards well planned, indication- and drug-specific development strategies involving fewer patients and studies, commented Deborah O'Neil, chief executive officer of NovaBiotics, a biotech company developing new classes of antimicrobials with novel mechanisms of action.

O'Neil told the *Pink Sheet* that the agency's initiative was welcome news as there are "simply not enough patients, time and investment" for studies that are "old school, statistically-perfect but [possible] only-in-theory." While there can be no "one-size-fits-all" approach to the development of antibacterials, she said that "overly onerous clinical development pathways have been and continue to be a barrier to the development of any new drug in this space."

Several small- and medium sized companies in the EU united under the BEAM Alliance – Biotech companies in Europe combating AntiMicrobial Resistance - are working on novel and paradigm-shifting antibacterial programs, such as protecting the human microbiome, potentiating existing antibiotics, supporting the human immune system, addressing bacterial virulence or having a narrower spectrum.

Many of these stated novel approaches address high unmet medical needs in small patient populations and "require more flexible and focused trial designs," said BEAM Alliance vice-president Marc Gitzinger, who is also the CEO and co-founder of Swiss biotech firm BioVersys. In some cases, classical models to establish pharmacokinetics and pharmacodynamics on the basis of minimum inhibitory concentration (MIC) are no longer applicable, "as the approach works either on bacterial virulence or in supporting the human immune system," explained Gitzinger.

"We would also encourage discussion on novel endpoints that would take the focus beyond the individual patient outcome and consider what we call a 'population effect'," he told the *Pink Sheet*. "For example, can we protect from resistance development and dissemination by protecting the microbiome?"

EMA Is Talking To Companies

Antimicrobial resistance is a growing global health concern and there has been a "resurgence of activity" in the development of antibacterial agents in the recent past. Since the adoption of the two EMA guidelines, the agency said several new antibacterial agents have been approved in the EU and companies have sought scientific advice on more products under development.

> **Interactions between the EMA and sponsors have highlighted the need for more clarity on the preferred process for the development of antibacterials in the EU - Deborah O'Neil, chief executive officer, NovaBiotics**

During discussion with sponsors on new products, the agency said that agreement was reached on some aspects of clinical development programs that were important for program feasibility and conduct "but which differ from, or are not included in, current guidance." Also, it became apparent that there is a need to include a detailed explanation of the indications that may be supported by various clinical development programs for antibacterial agents expected to address an unmet need.

O'Neil said that these interactions between the EMA and sponsors have understandably flagged the need to update the existing guidelines and provide more clarity on the preferred process for the development of antibacterials in the EU.

She noted that NovaBiotics and other companies developing novel non-antibiotic antimicrobials are particularly interested in the EMA's proposal on the possible removal of the "susceptibility testing interpretive criteria" from the summary of product characteristics (SmPC), which may be especially relevant in cases where *in vitro* susceptibility testing might not be predictive of a drug's performance in the clinic.

The BEAM Alliance is also involved in active discussions with the EMA and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to work on feasible and novel pathways to study innovative antibacterial treatment and prevention approaches. The alliance welcomed the opportunity to hold further dialogue on updating the EMA guidelines to support clinical trial design "that would unveil the true value of these much-needed novel approaches."

The EMA, for its part, wants to ensure that its guidance on this topic is clear, integrated and up to date. The new core guidance would help:

- Clarify which are the preferred and less-favored options for clinical programs of antibacterial agents expected to address an unmet need and provide an explanation of the indications that could result from different programs.
- Clarify clinical data requirements to support new combinations of known beta-lactam agents with new beta-lactamase inhibitors expected to address an unmet need.
- Reflect "points of alignment" agreed with US and Japanese regulators in relation to primary analysis populations, non-inferiority margins and some other aspects of trial designs to support some of the major infection-site specific indications. (Also see "AMR Threat Prompts EU, US And Japan To Join Forces To Align Data Requirements For New Drug Developers" - Pink Sheet, 13 Jun, 2017.) (Also see "EU, US, Japan Further Align Clinical Trial Requirements For

Certain New Antibiotics" - Pink Sheet, 20 Nov, 2017.) O'Neil said the alignment of the EMA guideline with the US Food and Drug Administration and the Japan's Pharmaceuticals and Medical Devices Agency is important "as the data from each territory should at least be relevant for [the] registration" of the medicinal product in each other's region. This will also ensure that companies "do not have to invest in fully stand-alone development programmes in each territory," she added.

Clarify considerations for the acceptance of single pivotal studies to support infection-site specific indications and pathogen-specific indications.

Offer guidance on clinical trials to support indications of uncomplicated urinary tract infections and uncomplicated gonorrhea.

Clarify the content of sections 4.4 and 5.1 of the SmPC.

The EMA is also planning to remove text in relation to pharmacokinetics and pharmacodynamics, tuberculosis and pediatric development and replace them with appropriate cross-references to its guidelines on these topics, namely:

Guideline on the use of PK-PD in the development of antimicrobial medicinal products (EMA/CHMP/594085/2015).

Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to mycobacterium tuberculosis (EMA/CHMP/EWP/14377/2008 Rev 1).

Draft addendum to the guideline on the evaluation of medicinal products indicated for bacterial infections to address paediatric-specific clinical data requirements (EMA/187859/2017). (Also see "EMA Consults On Extrapolation Considerations For Antibacterial Agents To Treat Pediatrics" - Pink Sheet, 10 Apr, 2018.)

Stakeholders have until Sept. 13 to comment on the EMA's proposal. O'Neil said it was essential that all stakeholders responded to shape these guidelines for the future. Also, she suggested that the EMA should commit to keep revising its guidance in response to unmet needs, and take into account the next generation of novel antibacterial molecules that are already in development.

From the editors of Scrip Regulatory Affairs.