ESSENCE

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

**PHARMACOLOGY BULLETIN**

JULY-AUGUST 2021, ISSUE 11

## FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the eleventh issue of ESSENCE.

On 23 Aug 2021, headlines across the world announced that FDA approval of the Pfizer-BioNTech as the first COVID vaccine. To many people including health care professionals, the news came as a surprise. This was because by that time more than 300 million doses of the vaccine had already been administered across the world since the FDA gave an Emergency Use Authorization (EUA) to this vaccine on 11 Dec 2021. The current issue discusses the process of EUA and the various criteria essential for EUA.

Optimizing the use of antibiotics is critical to effectively treat and prevent infections, protect patients from harms caused by unnecessary antibiotic use and combat antibiotic resistance. Antibiotic Stewardship Programs (ASPS) can help clinicians improve clinical outcomes and minimize harms by improving antibiotic prescribing. The current issue highlights the crucial role 'antibiotic stewardship' plays in the regard especially in surgical prophylaxis.

As always, this issue of ESSENCE also discusses the important developments in the field of therapeutics and drug safety. Finally, readers can test their knowledge with the cross word on 'Drugs causing Haemolytic anaemia'.

Happy Reading and Stay Safe.

Jai Hind.

**Chief Editor:** Dr. Sushil Sharma
**Editor:** Dr. Arup Kumar Misra
**Co-Editors:** Dr. Madhavrao, Dr. Gaurav M Rangari

Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh at email id: pharmacology@aiimsmangalagiri.edu.in

## Emergency Use Authorisation (EUA) of a Drug/Medical Product :

Before a drug/medical product can be used, approval of the FDA is a mandatory requirement. FDA approval requires that clear evidence is presented to prove that the drug is safe, effective, and potent. This process requires huge amounts of data, and it may take years for the FDA approval to come through. However, in certain critical situations, FDA may authorize the use of a drug/medical product based on limited data in the larger public health interest.

The FDA defines EUA as "an expedited authorization and use of an unapproved product in a declared emergency involving a chemical, biological, radiological, or nuclear (CBRN) agent." These can include drugs, biological products, and devices that have the potential "to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by a CBRN agent when there are no adequate, approved, and available alternatives."

**SATISFYING THE EUA CRITERIA:**

The FDA has established four broad criteria that must be met in order to participate in the EUA program and be granted an EUA:

a. Presence of a serious or life-threatening condition

b. Evidence of effectiveness

c. Risk-benefit analysis (safety)

d. No other alternatives to address the life-threatening condition

**A. Presence of Life-Threatening Condition**

Specifically, for the FDA to issue an EUA, the CBRN agents must be capable of causing a serious or life-threatening disease or condition. The COVID-19 pandemic clearly fulfilled these criteria paving way for the FDA to explore the avenue for EUA.

**B. Evidence of Effectiveness**

For an EUA, the requirement is a lower standard than would be typically applied in a formal regulatory submission, specifically only requiring that the proposed drug "may be effective" to prevent, diagnose, or treat serious or life-threatening diseases or conditions that can be caused by a CBRN agent. The FDA assesses the potential effectiveness on a case-by-case basis and if, based on the totality of the scientific evidence available, it is reasonable to believe that the product may be effective for the specified use, the FDA may authorize its emergency use, provided that other statutory criteria for issuing an EUA also are met. Based on the clinical trials the COVID vaccine were able to satisfy this criterion.

**C. Risk-Benefit Analysis**

In determining whether the known and potential benefits of the product outweigh the risks, the FDA looks at the totality of the scientific evidence available to make an overall risk-benefit determination. Evidence could arise from a variety of sources available for FDA consideration, such as results of domestic and foreign clinical trials, in vivo efficacy data from animal models, and in vitro data.

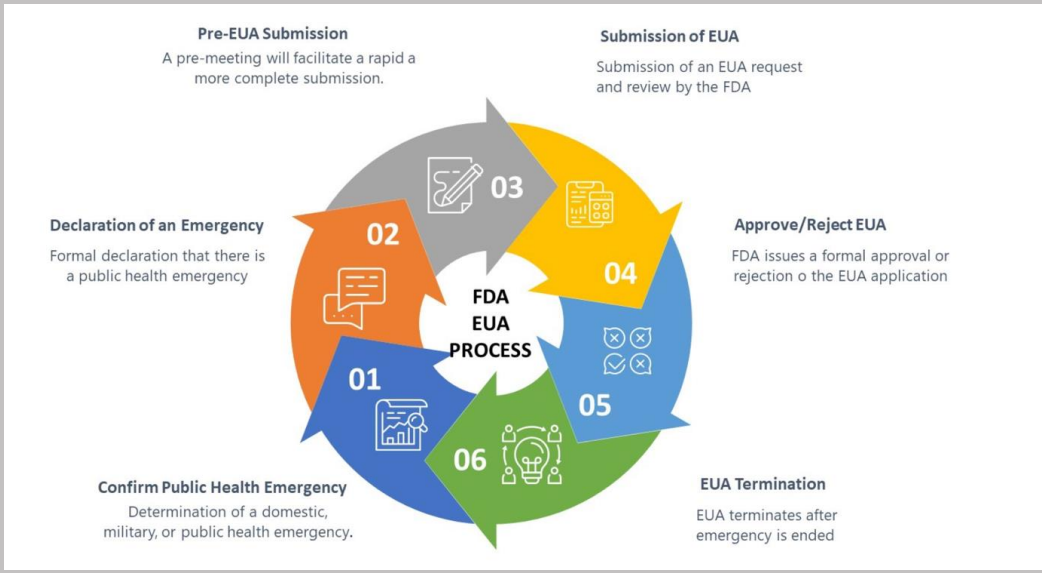
The FDA recommends that a request for an EUA include a discussion of the candidate product's known and potential risks and benefits, which includes a synthesis of the data and information from all available sources and must include contraindications if any.

Although time is of the essence in a national emergency, rushing ahead and putting patients at increased risk is a paramount concern for the FDA. Generally, the FDA recommends that data submissions for pre-EUA activities follow recommendations for submitting pre-IND, IND, and device pre-submissions.

D. **No Other Alternatives**

For the FDA to issue an EUA, there must be no adequate, approved, and available alternative to the candidate product for diagnosing, preventing, or treating the disease or condition.

The FDA guidance defines six elements of the EUA process as shown in Figure 1 below:




**EUA Submission:**

The EUA template is available for download from the FDA website. Although, the exact type and amount of data needed to support the EUA may vary depending on the nature of the declared emergency or threat of emergency and the nature of the candidate product. Typically, a EUA request must include a well-organized summary of the available scientific evidence regarding the product's safety and effectiveness, risks and benefits, and any available, approved alternatives to the product. The FDA may seek additional data and information on a case-by-case basis to ensure that the statutory criteria for issuance of an EUA are met.

**EUAs Expire with The Emergency:**

It is important to realize that a drug approved under a EUA does not signify FDA approval, licensure, or clearance. Once the emergency is de-notified, the EUA expires automatically. However, the sponsors can continue to develop their products, generate more data and can work toward full FDA approval after the termination of the emergency.

**References:**

1. Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholder (Office of Counterterrorism and Emerging Threats) https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

## Recent new/Update from the world of medicines ….

**Reversal of lung fibrosis in mouse model suggests a novel therapeutic target for pulmonary fibrosis**

Researchers have reversed lung fibrosis in a mouse model of idiopathic pulmonary fibrosis. Mice were given Bleomycin for 12 days to establish lung fibrosis, and then treated daily until 21 days with ABT-199 (Venetoclax) a medication approved by the USFDA for use in several forms of leukaemia. Control Bleomycin mice had lung fibrosis with widespread collagen deposition. The Bleomycin mice that received ABT-199 had normal lung architecture at 21 days and no collagen deposition. These results suggest a novel therapeutic target to reverse fibrotic remodelling in the lungs.

**Semaglutide is a Promising Drug Treatment for Chronic Weight Management**

Semaglutide received FDA approval for the treatment of chronic weight management in adults. Semaglutide is a GLP-1 agonist and is already approved for the treatment of Diabetes Mellitus. The drug is indicated in patients with BMI of 27 kg/m2 who have atleast one weight related ailment such as type 2 DM, Hypertension, or Dyslipidaemia alongside lifestyle interventions. Such interventions include a reduced calorie diet, such as establishing a 500 kcal deficit per day, and average physical activity of 150 minutes per week. . Semaglutide, is given as Sub-cutaneous injection and is available in 0.25, 0.5, 1.0, 1.7, and 2.4 mg strengths for titration purposes. The dose has to be increased gradually over a period of 16 to 20 weeks to 2.4 mg once a week dose to minimise GIT adverse effects.

## Be Cautious…. Drug Safety Alerts

| S. No. | Drug | Safety Alerts |
|---|---|---|
| 1. | Thalidomide | Progressive Multifocal Leukoencephalopathy (PML) |
| 2. | Ritodrine and Magnesium Sulfate | Hyperkalaemia |
| 3. | Amitriptyline | Eosinophilia and Systemic symptoms |
| 4. | Clopidogrel | Hypertension |
| 5. | Fluoroquinolones | Heart Valve Regurgitation |
| 6. | Indapamide | Rhabdomyolysis |

Surgical site infections (SSIs) are the most common component of nosocomial infections. Surgical prophylaxis is important to prevent surgical site infections by using an antimicrobial agent that is safe, cost-effective, and has a spectrum of activity that covers the most common pathogens for surgical procedures. Surgical prophylaxis is given to achieve appropriate serum and tissue concentrations of the antimicrobial agent prior to the time of incision and throughout the duration of the surgical procedure. Patients who develop SSIs are up to 60% more likely to spend time in an intensive care unit, five times more likely to be readmitted to the hospital, and two times more likely to die than are patients without an SSI. Health care costs are substantially increased for patients who develop SSIs. Surgical prophylaxis has become the standard care for contaminated surgery and clean contaminated surgery and for surgery involving insertion of artificial devices.

**Principles and Goals for Surgical Antibiotic Prophylaxis**

Antimicrobial agent for surgical prophylaxis should (1) Prevent Surgical Site Infections, (2) Reduce the cost and duration of treatment, (3) Prevents adverse effects and (4) have no adverse consequences on the microbial flora of the patient or the hospital. To achieve these goals, an antimicrobial agent should be (1) active against the bacterial flora most likely to contaminate the surgical site, (2) narrow spectrum antibiotic and avoid antibiotics used for serious sepsis, (3) less expensive, (4) given in an appropriate dosage and time, (5) administered for a short duration and (6) have minimal adverse effects.

**Choice of Antibiotics:**

The antimicrobial agent should have activity against the most common surgical-site pathogens. The most predominant organisms causing surgical infections are S. aureus and coagulase-negative staphylococci (e.g., Staphylococcus epidermidis) belonging to skin flora. In clean-contaminated procedures, the predominant organisms include gram-negative rods and enterococci in addition to skin flora. Agents that are FDA-approved for use in surgical antimicrobial prophylaxis include intravenous cephalosporins like Cefazolin, Cefuroxime, Cefoxitin or Cefotetan; oral Tinidazole (if anaerobic infection is likely); intravenous Gentamicin; intravenous or rectal Metronidazole (if anaerobic infection is likely); intravenous Flucloxacillin (if methicillin-susceptible staphylococcal infection is likely) and intravenous Vancomycin (if MRSA infection is likely). Alternatives to cephalosporins; with beta-lactam allergy, there are Vancomycin and Clindamycin. On the basis of local antimicrobial resistance patterns and institutional incidence of infections caused by organisms such as Clostridium difficile and Staphylococcus epidermidis, Vancomycin and Clindamycin are appropriate alternatives to beta-lactams.

In surgical patients, there is a wide range of organisms which have the probability of causing infection but SSI is usually caused due to a small number of common pathogens. Antibiotics should be used only for those organisms that are expected in the operative site. The antibiotics chosen must be disease-specific and should have antimicrobial susceptibility. The antibiotic should be used on the basis of its resistance in the hospital and drug costs. Narrow spectrum antibiotic which are less expensive should be the first choice for prophylaxis during surgery.

**Selection and Dosing:**

A single standard therapeutic dose of antibiotic is sufficient for prophylaxis under most circumstances. The drug dosing should be weight-based. As obese persons are at increased risk for surgical site infection therefore the pharmacokinetics of drugs may be altered in obese patients.

**Timing and Route of Antibiotic Administration:**

Antibiotic takes an approximate time to reach an effective concentration in the tissue that reflects its pharmacokinetic profile and the route of administration. Antibiotic prophylaxis for surgery is usually preferred to be given within one hour before incision except for Fluoroquinolone or Vancomycin, which are given within two hours prior to surgical incision. The timing of dosing is important as most Beta-lactams have short half-lives hence it should be given within one hour prior to incision.

On the other hand, if the antibiotic prophylaxis is administered too late or too early then the efficacy of the antibiotic is reduced and that may increase the risk of surgical site infections. Prophylaxis given three hours after the start of the operation significantly reduces its effectiveness. Additional doses are strongly recommended during intraoperative procedures of longer duration where time required is approximating two times the half-life of the drug. This corresponds with redosing antimicrobials at a frequency of one interval shorter than usual.

Intravenous route is most commonly used than intramuscular as peak tissue level can be achieved by this route. Other routes like oral or rectal antibiotics are given earlier to achieve tissue concentration. They must be given 2-4 hours before the incision. Topical antibiotics are not recommended except for ophthalmic or burn surgeries. On the other hand, administration of fluoroquinolones by the oral route achieves comparable serum and tissue levels to antibiotic prophylaxis via the IV route.

**Duration of Antibiotic Administration:**

Antibiotics prophylaxis beyond wound closure is unnecessary as it leads to emergence of resistant bacteria strains. It is unlikely that further benefit is attained by additional doses of antibiotic beyond wound closure and post-operative prophylaxis is not recommended. A single standard dose of antibiotic is sufficient for prophylaxis for most clean surgeries. Duration of antibiotic prophylaxis for surgery must be discontinued within 24 hours of the procedure. If prophylaxis is extended beyond the duration of surgery, antibiotics should be discontinued within 24 hours unless otherwise specified. American Society of Health-System Pharmacists (ASHP) recommends continuing prophylaxis for up to 72 hours for cardiac surgery. An additional intraoperative dose of antibiotic is recommended for surgeries longer than four hours when using an antibiotic with short half-life like cefuroxime, cefazolin, etc.

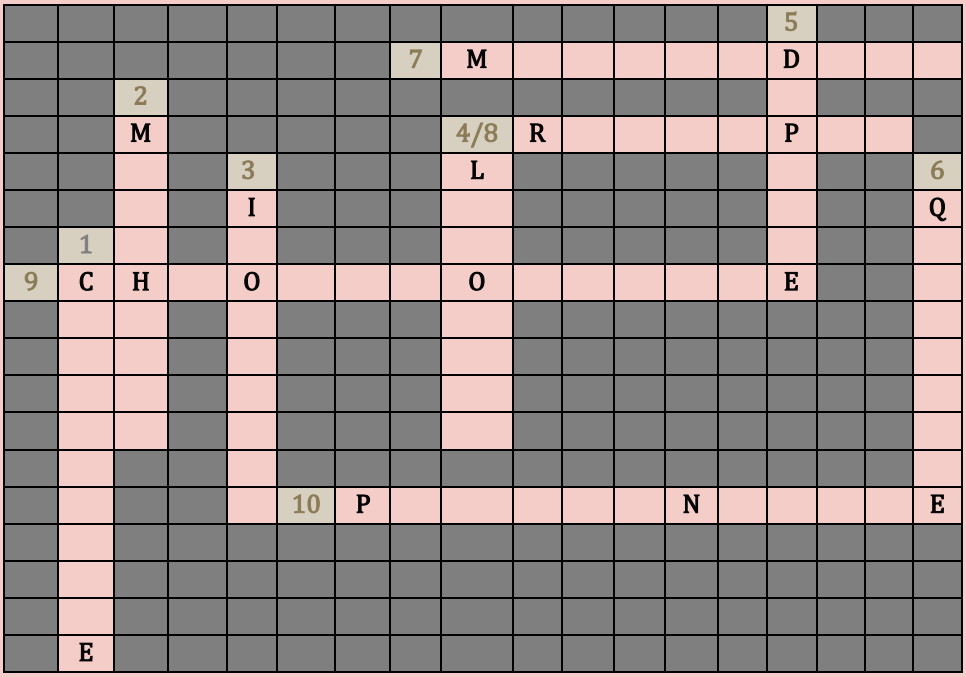
**Conclusion:**

Surgical antibiotic prophylaxis is an effective management for reducing postoperative infection provided that the antibiotic is given at the correct time, cover the organism that are likely to be encountered during particular surgery and given for appropriate duration. The selection of antimicrobial prophylaxis should be narrow spectrum that is not use in sepsis to avoid selection of resistance bacteria. It should have the least impact on the normal bacterial flora of the patient and the microbiologic ecology of the institution or hospital.

| S. No. | Drug | Pharmacological Class | Indication | Dosage |
|---|---|---|---|---|
| 1. | Finerenone | Non- steroidal selective mineralocorticoid receptor antagonist | Chronic kidney disease (CKD) associated with type 2 diabetes (T2D) | 20 mg orally OD |
| 2. | Fexinidazole | Nitroimidazole antibacterial | African sleeping sickness | 600 mg orally OD |
| 3. | Belumosudil | Kinase inhibitor | Chronic graft-versus-host disease (cGVHD). | 200 mg orally OD |
| 4. | Odevixibat | Ileal bile acid transport (IBAT) inhibitor | Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC). | 40 mcg/kg orally OD |
| 5. | Anifrolumab | Interferon (IFN) receptor antagonist | Systemic lupus erythematosus (SLE) | 300 mg IV infusion over 30 min every 4 weeks |
| 6. | Belzutifan | Selective inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α) | Von Hippel-Lindau Disease | 120 mg Orally OD |
| 7. | Difelikefalin | Selective peripheral kappa opioid receptor agonist | Pruritus associated with chronic kidney disease | 65 mcg IV |
| 8. | Lonapegsomatropin-tcgd | Human growth hormone | Paediatric Growth Hormone Deficiency | 0.24 mg/kg SC weekly |
| 9. | Avalglucosidase alfa-ngpt | Hydrolytic lysosomal glycogen-specific enzyme | Pompe Disease | 20 mg/kg IV |
| 10. | Asparaginase Erwinia Chrysanthemi (recombinant) | Asparagine specific enzyme | Acute Lymphoblastic Leukaemia | 25000 IU/m2 IM or IV |

## Crossword Puzzle…

**Hint:** *Drugs Causing 'Hemolytic Anemia'*




| **Downward** | **Across** |
|---|---|
| 1. Third generation Cephalosporin (*11*)<br>2. Alkylating Anticancer drug, effective in multiple myeloma (*9*)<br>3. First line anti-tubercular drug associated with peripheral neuritis as an ADR (*9*)<br>4. Dopamine precursor used in Parkinson's disease (*8*)<br>5. Drug effective against *P. falciparum, Toxoplasma gondii, M. leprae and Pneumocystis jirovecii* infections (*7*)<br>6. Class I anti-arrhythmic drug with $Na^+$ channel blocking properties (*9*) | 7. Centrally acting sympatholytic; Good safety profile in the treatment of hypertension in pregnancy (*10*)<br>8. Drug used clinically in TB as well as in Leprosy *(8)*<br>9. Anti-psychotic agent with highest α blocking property, acts primarily by blocking $D_2$ receptors *(14)*<br>10. Class I anti-arrhythmic drug; also has local anesthetic activity *(12)* |

**Answers:**

**Downward**

1. Ceftriaxone 2. Melphalan 3. Isoniazid 4. Levodopa 5. Dapsone 6. Quinidine

**Across**

7. Methyldopa 8. Rifampin 9. Chlorpromazine 10. Procainamide