"A COMPREHENSIVE AND COMPARATIVE STUDY ON REGULATIONS OF MEDICAL COUNTERMEASURES IN USA AND INDIA"

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ABSTRACT:

The current scenario of emerging infectious diseases and CBRN threats to health has increased within recent past years and threatens to increase in near future. Medical Countermeasures has attracted interest from regulatory authorities, particularly after the world trade center and anthrax attacks in the year of 2001, resulted in to the guidelines of medical countermeasures in USA. The National disaster Management Authority of India has issued a guideline of Biological warfare agents in 2008. These address the full flow chart starting from the risk assessment to the surveillance plan for minimizing the risks. This article presents an overview of regulatory framework in USA and INDIA.

Index terms: Medical countermeasures, Countermeasures for public health emergencies, Emergency medicine, Biological warfare agents.

INTRODUCTION:[1]

- Medical countermeasures are regulated products that may be used in the condition of public health crisis and emergency situation raised by the terrorist attack with the chemical, Biological, and Radiological or Nuclear substances or naturally emerging infectious diseases.
- Medical countermeasures can be used to diagnose, prevent, protect from, or treat conditions associated with chemical, biological, radiological, or nuclear (CBRN) threats, or emerging infectious diseases.
- MCMs can include protections for and responses to many exclusive kinds of events (e.g. diseases, outbreaks, natural disasters, terrorist attacks).

- Medical countermeasures are typically disbursed or administered with the aid of fitness care suppliers and public health responders under reputable federal, state, and/or native emergency response plans.
- Emergency medicines, an area of practice based totally on the expertise and abilities necessary for the prevention, analysis and administration of acute and urgent components of sickness and injury that affects the patients of all age groups with a full spectrum of periodic undifferentiated physical and behavioural disorders.
- This includes to provide the proper medical response for patients that are searching for urgent medical care.
- Medical countermeasures are developed on a international scale to mitigate and prevent pandemic disorder agents as well as chemical, biological and radiological threats, each accidental and intentional.
- A broad definition of MCMs provided to prevent and alleviate the health effects of biological agents by the White House Office of Science and Technology Policy, which states three types of countermeasures.
    1. Pharmaceutical and Biological countermeasures. (e.g. vaccines, antimicrobials, and antibody preparations)
    2. Non-pharmaceutical scientific countermeasures. (e.g. Devices, Ventilators, Personal protective equipments such as gloves and face masks.)
    3. Public health interventions. (e.g. contact and transmission interventions, social disaffection, and community protecting.)

- Different names of Medical Countermeasures throughout different Jurisdiction :
    1. Medical countermeasures (USA,Japan)
    2. Emergency medicine / Crisis preparedness and response (EU)
    3. Emergency Preparedness and response (Canada)
    4. Emergency medicine and disaster preparedness (India)

REGULATORY FRAME WORK IN USA:[2-4]

- The Public Health Emergency Medical Countermeasures Enterprise, otherwise known as the PHEMCE, was established by the U.S. Department of Health and Human Services (HHS) in 2006 to coordinate Federal efforts to enhance preparedness and response for chemical, biological, radiological, and nuclear (CBRN) threats, pandemic influenza, and emerging and infectious diseases.
- Defining and prioritizing requirements for public health emergency medical Countermeasures
- Focusing research, development, and procurement activities on the identified Requirements
- Establishing deployment and use strategies for medical countermeasures in the Strategic National Stockpile.

PHEMCE AGENCIES:

ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research And Development Authority
CDC	Centers for Disease Control
DHS	Department of homeland security
DoD	Department of Defense
FDA	Food and Drug Administration
NIH	National Institute of Health

- This Mission Components Include:
  - Requirements Setting
  - Early Stage Research
  - Advanced Development/Manufacturing
  - Regulatory Science Management:
  - Procurement / Inventory Management / Stockpiling
  - Response Planning, Policy, Guidance and Communication
  - Deployment / Distribution / Dispensing / Administration
  - Monitoring / Evaluation / Assessment

PRODUCT DEVELOPMENT UNDER ANIMAL RULE:

- The Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) added a new section 565(d) of the FD&C Act to require that FDA establish a procedure for a sponsor or applicant developing "a countermeasure for which human efficacy studies are not ethical or practicable, and that has an approved investigational new drug application or investigational device exemption" (IND and IDE, respectively) to request and receive two meetings with FDA – one meeting to discuss "proposed animal model development activities" and a second meeting prior to initiating pivotal animal studies.

- Drugs evaluated for efficacy under the Animal Rule should be evaluated for safety under the existing requirements for establishing the safety of new drugs.

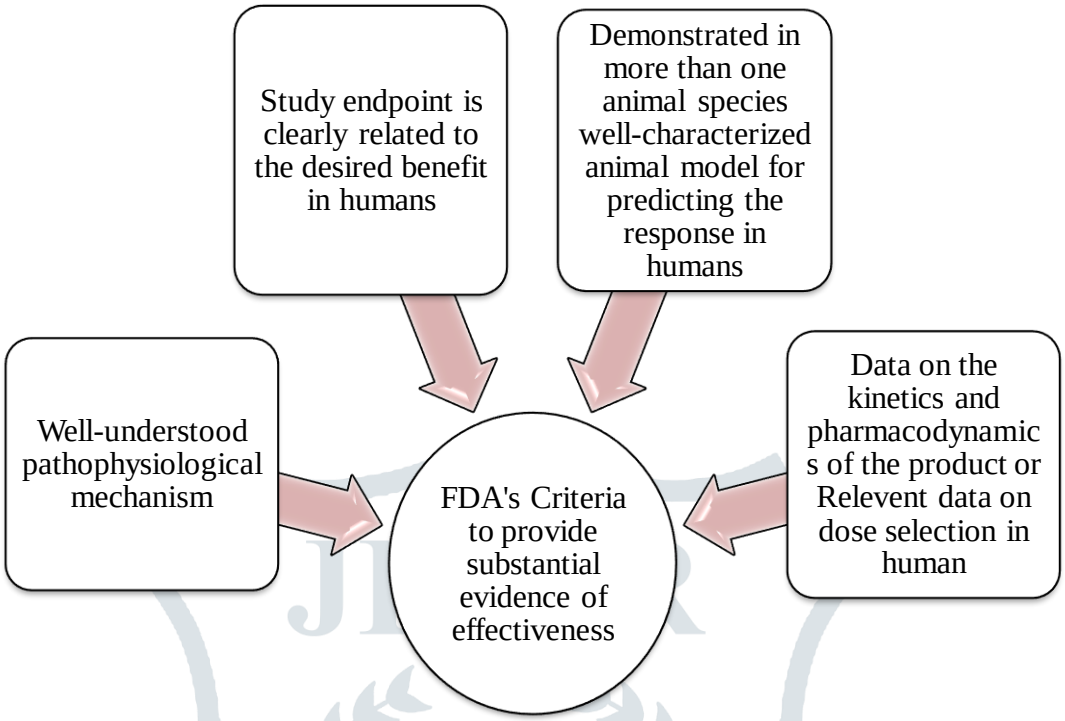

Fig.1 FDA Criteria for evaluation

- Approval of a drug under the Animal Rule imposes three additional requirements, which are summarized below:

1. Postmarketing studies (e.g., field studies) to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical (i.e., in the event an emergency arises and the drug is used). A plan or approach to conducting such a study must be included with the new drug application (NDA) or biologics license application (BLA).
2. Restrictions to ensure safe use, if needed (e.g., restricting distribution to facilities or health care practitioners with special training, requiring specified types of follow up, or imposing record keeping requirements).
3. Information to be provided in the labeling to patient recipients that explains that for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone. This information must be provided before administration or dispensing, if possible.

- Safety signals identified from animal studies or human trials should be characterized.

Figure: Elements of Investigational Drug and Selection of an effective dose in Humans

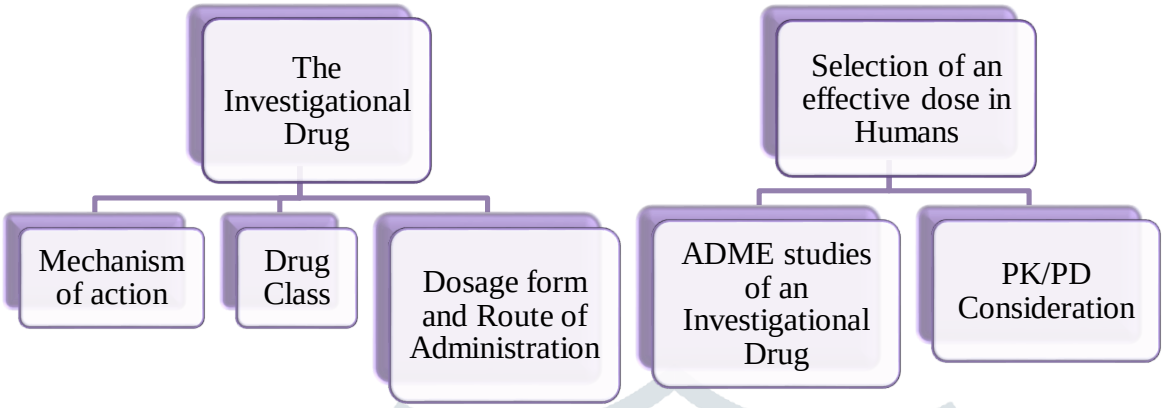

Table. Summary of PAHPRA's MCM Emergency Preparedness and Response Provisions

MCM Emergency Preparedness and Response Provisions	MCM Category	FD&C Act Section
Amendments to the Emergency Use Authorization (EUA) Authority	* *Unapproved MCMs* * *Unapproved uses of approved MCMs*	§ 564
Determinations for EUA issuance		§§ 564(b)(1)(A)-(D)
Duration of HHS EUA declaration		§ 564(b)(2)
EUAs issued for preparedness purposes		§ 564(b)(1)
Data collection time period		§ 564(e)(1)(B)(iii)
Categorization of in vitro diagnostics (IVDs)		§ 564(m)
New Emergency Use Authorities (No EUA)	* *Approved MCMs only*	§§ 564A & 505-1
Emergency use instructions (EUI)		§ 564A(e)
Emergency dispensing orders		§ 564A(d)
Expiration dating extensions		§ 564A(b)
CGMP waivers		§ 564A(c)
REMS waivers		§ 505-1
New Pre-Positioning Authority	* *Approved MCMs* * *Unapproved MCMs*	§ 564B

AN EMERGENCY USE AUTHORIZATION:

- The EUA authority is a legal mechanism that allows FDA to help strengthen the nation's public health protections against CBRN threats by facilitating the availability of MCMs needed during public health emergencies.
  - Under the FD&C Act, the FDA Commissioner can allow either

    (a) The *use of an unapproved medical product* (e.g., drug, vaccine, or diagnostic device) or

    (b) The *unapproved use of an approved medical product* during an emergency to diagnose, treat, or prevent a serious or life-threatening disease or condition caused by a CBRN agent if certain statutory criteria are met.
  - When scientific evidence is available to support such a use in an emergency, issuing an EUA enables response stakeholders to use, or prepare to use, an MCM without violating the FD&C Act.

EUA MEDICAL PRODUCTS:

1. **Criteria for Issuance**
   a. Serious or Life-Threatening Disease or Condition
   b. Evidence of Effectiveness
   c. Risk-Benefit Analysis
   d. No Alternatives

2. **Categories of Products**

- The FDA reviews EUA requests on a case-by-case basis using the scientific data available at the time and the circumstances of the emergency.

1. Preparedness and Response
2. Information Recommendations
   a. Summary of Recommended Information and/or Data
   b. Recommended Safety Information
   c. Recommended Effectiveness Information
   d. Other Data Considerations
   e. Discussion of Risks and Benefits
3. Format of Submissions

FDA PROCESSING OF AN EUA REQUEST:

a. Prioritization of Requests
b. Review of Requests to Issue an EUA
c. Disposition of Requests

CONDITIONS OF AUTHORIZATION:

1. Information Relating to the EUA Product
   a. Information for Health Care Professionals or Authorized Dispensers
   b. Information for Recipients
2. Monitoring and Reporting of Adverse Events
3. Records
4. Additional Conditions of Authorization:
   - Distribution and Administration
   - Advertising
   - Duration and Termination

➢ The dispensing of MCM through Open and/or Closed Points of Dispensing (PODs).

REGULATORY FRAMEWORK IN INDIA:[5-6]

➢ The National Disaster Management Authority (NDMA) has begun preparedness, but concedes more cooperation is needed from companies and communities. To strengthen the existing eight battalions of the National Disaster Response Force, each consisting of 1000, two more battalions have been sanctioned. Half of the existing force is specifically trained to deal with chemical, biological, radiological, and nuclear (CBRN) threats.

➢ NDMA has also asked the state governments to get part of the state forces trained in such areas. The revised International Health Regulations came into force in India in June 2007. The regulations will help to ensure that outbreaks and other public health emergencies of international concern are detected and investigated more rapidly and that collective international action is taken to support affected states to contain the emergency, save lives, and prevent its spread.

GUIDELINES FOR BIOLOGICAL DISASTER MANAGEMENTS:

A) Legislative Framework:

The important means to develop a robust though flexible legal framework include:

1) Legal Framework
2) Policy, Programmes, Plans and Standard Operating Procedures
3) Institutional and Operational Framework

B) Prevention of biological Disaster:

1) Vulnerability Analysis and Risk Assessment
2) Environmental management:
   a. Water supply

b. Personal Hygiene
c. Vector Control
d. Burial/Disposal of the dead

3) Prevention of Post disaster epidemics
4) Integrated disease surveillance system
5) Pharmaceutical Interventions: Chemoprophylaxis, Immunisation and Other Preventive Measures
6) Non Pharmaceutical Interventions
   a. Social Distancing Method
   b. Disease Containment by Isolation and Quarantine Methodologies
7) Bio-safety and security measures
8) Protection of important buildings and offices

C) Preparedness and Capacity Development:

1) Establishment of Command, Control and Coordination Functions
2) Capacity development
   a. Human resources management
   b. Training and Education
   c. Community Preparedness
   d. Documentation
   e. Research and development

D) Critical Infrastructure

1) Network of Laboratories
2) Bio monitoring
   a. Identification of causative agents
   b. Detection
   c. Moleculer techniques in early detection and identification
   d. Bioluminescence and biofluorescence
   e. Biosensors
   f. Bioprobes
   g. Molecular and other recent techniques
3) Technical and scientific institutions
4) Communication and networking
   a. Emergency Communication network
   b. Health Network

c. Mobile tele Health
d. Through Print and Electronic media
e. NGOs as a Part of BDM netweork
f. Role of International Organizations

5) Public-Private Partnership

E) Medical Preparedness

1) Hospital DM plan
2) Mobile Hospitals and Mobile Teams
3) Stockpile of Antibiotics and Vaccines
4) Public Health Issues

F) Emergency Medical and Public Health response

1) C&C for Medical and Public Health response
2) Emergency medical response
   a. Transportation of Patients
   b. Treatment at Hospitals
   c. Domiciliary Care
3) Public Health Response
   a. Outbreak Investigation
   b. Instituting Public Health Measures
   c. Risk Communication
   d. Psycho-social care
   e. Post-outbreak surveillance
   f. Media
   g. Inter sectoral coordination
   h. Monitoring
   i. Evaluation

G) Management of Pandemics

H) International Corporation

POTENTIAL THREATS FROM EXOTIC AND EXISTING INFECTIOUS DISEASES

Among the eight to ten globally recognised, most harmful TADs which can inflict enormous losses on livestock of a country or region in a short span of time, five are existing in the country, e.g., FMD, PPR, Newcastle disease, hog cholera and bluetongue.

CONSEQUENCES OF LOSES IN THE ANIMAL HUSBANDRY SECTOR

The consequences of loss of livestock in large numbers are predictable. These are primarily:

i) Food scarcity due to shortage of animal origin food, e.g., milk, meat and eggs.

ii) Economic crisis due to escalation of food prices (the value of milk output in India is equal to the combined value of paddy and wheat produced).

iii) Environmental contamination leading to epidemics due to massive animal mortality.

iv) Loss of valuable germ-plasm and biodiversity.

v) Loss of employment starting from primary producers, down the food processing and marketing chain.

vi) Loss of traction power, shortage of manure.

vii) Emotional shock to animal owners.

PRESENT STATUS AND CONTEXT:

1) Legislative and regulatory frame work:

❖ **International :**

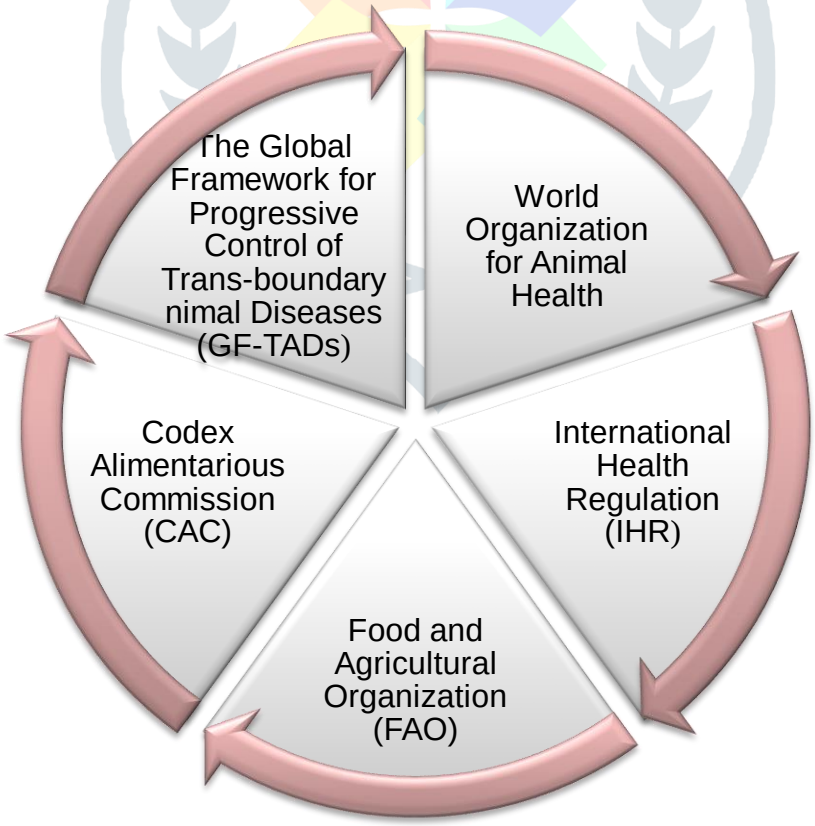

Figure: Intergovernmental and UN Organizations

TIMELINES FOR REGULATORY APPROVALS

Table. Regulatory approval in india.

Agency/ Institutions	Approval	Time
Drug Controller General Of India (DCGI)	Regulatory approval for study Conduct in India	• Category A trial is approved using a fast-trac k process within 6 weeks after the required documentation. •Category B within 8 to 12 weeks.
Drug Controller General Of India (DCGI)	The license to import trial supplies	2 weeks addition
Ethics Committees (Indepedent body)	Local ethics committee approval by sites	6-8 weeks (in parallel)
		Total (parallel processing) 6-8 weeks- FAST TRACK (Category A) 16 weeks (Category B)
Directorate General of Foreign Trade (DGFT)	Permission to Export Biological Samples	Additional 2-4 weeks

COMPARISION:

Sr. No.	PARAMETERS	USA	INDIA
1.	**Different Names According to Jurisdction**	Medical Countermeasures (MCMs)	Emergency Medical Care Products
2.	**Regulatory Agency**	USFDA	CDSCO

3.	**Defination**	Medical countermeasures, or MCMs, are FDA-regulated products (biologics, drugs, devices) that may be used in the event of a potential public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/ nuclear material, or a naturally occurring emerging disease.	Any Medical Product or device that successfully Meets the equirement of the challenges of pandemics, and strengthen the existing Objectives National Disaster management Authority.
4.	**Regulation Year**	After 2001, USFDA Introduced the guidelines of MCM	The guideline to the cross border threats has been implemented in 2002. Guideline for integrated diseases has been implemented in year 2004.
5.	**Risk Assessment Agency**	ASPR	MOH&FW, DDMA
6.	**Agencies responsible for Research and Development**	PHEMCE, NIH, ASPR, CDC,	CDSCO, NDMA, CSIR
7.	**Financing Agencies**	BARDA	C&C
8.	**Defencive Agency**	DoD, DHS	DRDO

9.	**Approving Authority**	HHS, FDA Commissioner	DCGI
10.	**Regulations on Authorised use of un-approved product**	EUAs. Declaration and Termination	-
11.	**Time Period for Approval**	270-324 weeks	34-42 weeks
12.	**Programs started internationally**	MCMi, AQMP, GHSi, Us- India Strategic Dialogue on Bio-security, IHR(WHO)	Us- India Strategic Dialogue on Bio-security, HR(WHO)
13.	**Challenges in Development**	Considerable uncertainty regarding the development, so it remains Contingent upon Government funding, Unique Incentive Systems and advanced purchase agreements.	Manufacturers have little financial incentives to develop and produce such products.
14.	**Communication with public during Emergency**	Standerdised Emergency Management System,Incident Command System	Community preparedness by education and training for capacity building. Role of Media.
15.	**Communication in longer term after crisis**	Media organizations, Tele communications, Public Health Responders, Internal-Inter Agency Communication	Post-outbreak surveillance, Media, Inter sectoral coordination

16.	**Steps to provide medical care during Emergency**	• Requirements Setting • Early Stage Research • Advanced Development/Manufacturing • Regulatory Science Management: • Procurement / Inventory Management / Stockpiling • Response Planning, Policy, Guidance and Communication • Deployment / Distribution / Dispensing / Administration • Monitoring / Evaluation / Assessment	• Understanding risk • Inter-Agency Coordination • Investigation • Capacity Development • Financial Arrangements • Response
17.	**Areasneed development**	Disposal of remains, Behavioral health, Environmental health, Economic restoration	India needs a coordinate action plan to maintain a level of epidemiological intelligence to keep a track on our adversaries' biowarfare Programmes. This applies to terrorist outfits using available in-

			house acilities to develop such weapons. Specialised capabilities for CBRN management in hospitals are grossly inadequate/do not exist.
18.	**Examples**	Afliuria, ACAM2000	FluQuadri, Nasovac, Vaxiflu-S, BONT/A-LC

CONCLUSION:

Medical countermeasures are tremendous field for fulfilling the demanding necessities of emergency medical care to public health. Regulatory aspects of medical countermeasures are complex but do not block product development therefore straight regulations for medical countermeasures are necessary. In this study it is observed that countries like USA has stringent regulations to be followed. While countries like India regulations are covering many areas in terms of public health that needs to be followed strictly. In this way it is possible to develop new MCMs to meet the emergency need of CBRN threats and emerging infectious diseases.

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