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Comparision of Fixed Dose Combination Regulation of Japan, Europe, Usa With India

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ABSTRACT: This abstract compares the regulatory frameworks for fixed dose combinations (FDCs) in Japan, Europe, the USA, and India. FDCs, which combine multiple active ingredients into a single dosage form, face various global regulatory challenges. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) requires thorough clinical trials for efficacy, safety, and quality. Europe's European Medicines Agency (EMA) uses EU legislation for quality, safety, and efficacy assessments, with centralized or decentralized procedures across member states. The US Food and Drug Administration (FDA) employ a risk-based approach with rigorous pre- and post-market evaluations, including proving therapeutic superiority. India's Central Drugs Standard Control Organization (CDSCO) balances accessibility, affordability, and safety with clinical data and bioequivalence studies. Despite differing methods, all regions emphasize patient safety and therapeutic efficacy, highlighting the need for pharmaceutical companies to navigate these complex regulations for successful drug development and market entry.
KEYWORDS: Banned drugs, India, Regulatory framework, fixed dose.

I. INTRODUCTION

The World Health Organization (WHO) defines Fixed-Dose Combinations (FDCs) as products containing two or more active ingredients in a fixed ratio. These can be administered as single entity products given together or as a finished pharmaceutical product. FDCs are considered rational if they improve efficacy, reduce antimicrobial resistance, and decrease the occurrence of adverse effects while lowering therapy costs. The Central Drugs Standard Control Organization (CDSCO) outlines different approval pathways for FDCs based on their novelty and therapeutic claims.

Categories and Approval Criteria by CDSCO

1. **New Drug FDCs**:

If one or more ingredients are new drugs, the approval process mirrors that for new drugs, including clinical trials.

2. **New Combinations of Existing Drugs**:

When combining previously approved drugs for the first time, clinical trial data from other countries and regulatory status should be provided. If the combination has not been marketed before, detailed chemical and pharmaceutical data along with stability data are required.

3. **Modification of Existing FDCs**:

For changes in the ratio of active ingredients or new therapeutic claims, relevant rationale and published reports must be submitted. The approval depends on the nature of the claim and supporting data.

4. **Convenience Combinations**:

For FDCs where the ingredients have been used widely and the combination is primarily for convenience, stability and interaction data must be demonstrated. Generally, no additional clinical data are required.

European Medicines Agency (EMA) and UK Regulations

- **EMA**: FDCs are evaluated for clinical benefit, including improved efficacy, safety, and patient adherence. The combined safety profile of all active substances must be considered.
- **UK**: The Medicines and Healthcare products Regulatory Agency (MHRA) oversees FDCs, ensuring they are effective and safe. License

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applications can be processed through the EMA for Europe-wide approvals or directly via the MHRA for UK-specific licenses.

U.S. Food and Drug Administration (FDA) Regulations

- **Definition**: The FDA defines a combination product as any blend of drug, device, or biological products.
- **Approval Policy**: For fixed-combination prescription drugs, each component must contribute to the claimed effects. Combinations are evaluated for their safety and effectiveness, including special cases where components enhance safety or minimize abuse potential. If an FDC has not been recognized as effective, changes in formulation, labeling, or dosage may be proposed.

Regulatory Landscape in Japan

- **Pharmaceuticals and Medical Devices Agency (PMDA)** and **Ministry of Health, Labour and Welfare (MHLW)** oversee drug approvals in Japan. Since 2005, 73 new FDCs have been approved. These FDCs have improved patient convenience and adherence but raise concerns about potential confusion due to rapid increases in new FDCs.

General Problems with FDCs

- **Pharmacodynamic and Pharmacokinetic Issues**: Misalignment between drugs can reduce efficacy or enhance toxicity.
- **Chemical Compatibility**: Non-compatibility may affect shelf life and stability.
- **Drug Interactions**: Common metabolic pathways may lead to adverse interactions.
- **Dose Titration**: Challenges in fine-tuning doses of individual components.

FDCs in the Indian Market

- India has over 6000 FDCs, many of which lack adequate scientific justification. Some FDCs have been manufactured without proper approval from the Drugs Controller General of India (DCGI). Studies indicate that a significant proportion of FDCs available in India are not approved compared to those in regulated markets like the UK and USA.

Key Regulatory Terms and Concepts

- **Active Pharmaceutical Ingredient (API)**: The substance intended to have an effect in a therapeutic product.
- **Active Moiety**: The active therapeutic entity in the final formulation.
- **Co-packaged Product**: Products containing separate pharmaceuticals packaged together.
- **Finished Pharmaceutical Product (FPP)**: A product that has completed all stages of production and is ready for distribution.
- **Fixed-Dose Combination Finished Pharmaceutical Product (FDC-FPP)**: A final product containing two or more actives in a fixed ratio.

Data Required for Approval

1. **Common Documents**: Form 44, treasury challan, therapeutic rationale, chemical and pharmaceutical data, GMP certification, and post-marketing surveillance strategy.
2. **Category-Specific Requirements**:
   - **New Drug FDCs**: Data similar to new chemical entities.
   - **Existing Drug FDCs**: Comparative data from other countries, literature, and bio-equivalence studies.
   - **Changes to Existing FDCs**: Rationale for changes, clinical and in vitro studies, and stability data.
   - **New Dosage Forms**: Bio-equivalence studies and updated clinical data.

This comprehensive framework ensures that FDCs are evaluated rigorously to balance their benefits and risks, ultimately aiming to enhance patient care andtherapeutic effectiveness

II. LITERATURE REVIEW

These articles offer a comprehensive overview of fixed-dose combinations (FDCs) and their implications in different contexts. Here's a summary of each:

Summary of Fixed-Dose Combination (FDC) Therapy Research

Kalra et al., 2020: This review assesses the safety, efficacy, and tolerability ofFDCs in managing Type 2 Diabetes Mellitus (T2DM). Findings indicate that FDCs enhance patient adherence, reduce costs, and provide effective glycemic control. The review advocates for discontinuing irrational metformin FDCs banned in India and emphasizes the need for continuous

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education for primary care physicians and pharmacists to distinguish between rational and irrational FDCs.

Parveen et al., 2023: This article offers a comprehensive overview of FDC therapy, highlighting its advantages such as improved treatment outcomes, better adherence, and cost-effectiveness. It also addresses challenges related to safety, efficacy, drug interactions, and regulatory issues. The review aims to improve understanding among healthcare professionals, regulators, and patients by examining literature, clinical studies, and real-world examples.

McGettigan et al., 2015: This study discusses the regulatory landscape of FDCs in India, noting that many were unapproved before May 1, 2002, with NSAIDs, metformin, and anti-depressants being particularly affected. It underscores the need for stringent regulatory approval to ensure safety and efficacy.

Miranda et al., 2019: The ban on 328 irrational FDCs in India is viewed as a significant step toward strengthening healthcare policy, rather than a hindrance to the pharmaceutical industry. This move is seen as pivotal in advancing public health and regulatory standards.

Kikuchi et al., 2019: In Japan, the introduction of new FDC drugs since 2006 has improved patient compliance and prescription efficiency. However, this increase has also led to some confusion within the medical field, suggesting a need for better education and guidelines.

Tanavadeet al., 2016: The importance of FDCs for chronic diseases and HIV/AIDS is acknowledged, but the study calls for stricter approval guidelines and continuous research to ensure they benefit patients effectively.

Sawicki-Wrzasket al., 2015: FDCs are promising for enhancing efficacy and reducing adverse effects in complex diseases. Successful development requires collaboration between industry, regulatory bodies, and patients to address the challenges associated with these combinations.

Balasubramanian et al., 2014: This retrospective analysis emphasizes the need for regulatory guidelines in the Indian market for FDCs. It highlights the importance of evaluating safety profiles when combining established drugs and suggests a comprehensive analysis of global markets and the potential for promising new drugs
This summary encapsulates key points from the various studies, focusing on the benefits, challenges, and regulatory considerations of FDC therapy.

III. AIM AND OBJECTIVES

Aim:

This research seeks to explore the global landscape of banned Fixed Dose Combinations (FDCs), with a focus on comparing international regulatory frameworks to that of India. The study aims to investigate legal cases related to FDC bans, assess their market impacts, and understand the approval process and registration requirements for FDCs in India. The goal is to offer a comprehensive view of the regulatory, legal, market, and procedural dimensions of banned FDCs, ultimately aiding in the development of informed, evidence-based policies in the pharmaceutical industry.

Objectives:

1. Regulatory Comparison:Examine the regulatory environment surrounding banned FDCs globally and compare it with India's regulatory framework.
2. Legal Analysis: Analyze legal cases related to FDC bans to understand the judicial perspective and implications.
3. Market Impact: Assess the market impact of FDC bans across various countries to evaluate economic and industry effects.
4. Approval Process in India: Gain insights into the approval process and requirements for registering FDCs in India.

These objectives aim to provide a holistic understanding of the issues related to banned FDCs, supporting informed decision-making and policy development in the pharmaceutical sector.

IV. METHODOLOGY

DRUG APPROVAL PROCESS IN INDIA

In India, the drug approval process, overseen by the Central Drugs Standard Control Organization (CDSCO), includes:

1. **Pre-Application:** Prepare a dossier with preclinical and clinical data, manufacturing details, and labeling. Optional consultations with CDSCO may be sought.
2. **Submission:** Submit Form 44 along with the application fee (INR 15,000 or INR 50,000 depending on API approval status) and required documentation including therapeutic justification and clinical trial results.
3. **Review:** Expert committees like the Drugs Technical Advisory Board (DTAB) or Subject Expert Committees (SEC) review the

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application and clinical data. Additional trials may be needed for new drugs.
4. **Approval:** CDSCO issues a license for manufacturing and marketing based on the review, with specific conditions.
5. **Post-Market Surveillance:** Monitor safety through pharmacovigilance and ensure compliance with Good Manufacturing Practices (GMP) through regular inspections.
6. **Modifications:** Changes to formulation or manufacturing require a separate approval process.

DRUG APPROVAL PROCESS IN JAPAN

In the United States, the Food and Drug Administration (FDA) manages drug approval through these steps:

1. **Pre-Application:** Collect preclinical and clinical data. Optionally, conduct a pre-IND meeting with the FDA.
2. **IND Application:** Submit an IND application with preclinical data and clinical trial plans for FDA review.
3. **Clinical Trials:** Conduct Phase 1 (safety), Phase 2 (efficacy), and Phase 3 (large-scale effectiveness) trials.
4. **NDA Submission:** File a New Drug Application (NDA) with comprehensive clinical data, labeling, and manufacturing information.
5. **FDA Review:** The FDA reviews the NDA, involving expert evaluations.
6. **Approval:** If approved, the FDA issues a license for market entry.
7. **Post-Market Surveillance:** Monitor the drug for safety and efficacy, ensuring adherence to Good Manufacturing Practices (GMP).

This process ensures rigorous evaluation of drug safety and effectiveness before market approval.

DRUG APPROVAL PROCESS IN USA

In the U.S., the Food and Drug Administration (FDA) manages drug approval through these steps:

1. **Pre-Application:** Collect preclinical and clinical data; optional pre-IND meeting with the FDA.
2. **IND Application:** Submit Investigational New Drug (IND) application for review.
3. **Clinical Trials:** Conduct Phase 1 (safety), Phase 2 (efficacy), and Phase 3 (large-scale effectiveness) trials.
4. **NDA Submission:** File New Drug Application (NDA) with comprehensive data and labelling for FDA review.
5. **Approval:** FDA grants approval if regulatory standards are met.
6. **Post-Market Surveillance:** Monitor safety and compliance with Good Manufacturing Practices (GMP).
7. **Amendments:** Submit separate applications for any changes to the drug.

This process ensures thorough evaluation of drug safety and efficacy before market release.

DRUG APPROVAL PROCESS IN EUROPE

In Europe, the European Medicines Agency (EMA) manages drug approval through these steps:

1. **Pre-Application:** Prepare preclinical and clinical data; optional scientific advice from EMA.
2. **Submission:** File a Marketing Authorization Application (MAA) with data, manufacturing details, and labelling.
3. **Review:** EMA reviews the application, with evaluation by the Committee for Medicinal Products for Human Use (CHMP).
4. **Approval:** The European Commission grants marketing authorization based on CHMP recommendations.
5. **Post-Market Surveillance:** Monitor safety and effectiveness, ensuring Good Manufacturing Practices (GMP) compliance.
6. **Amendments:** Submit applications for changes to formulation or labelling.

This process ensures rigorous evaluation of drug safety and efficacy before market approval in Europe.

Banned FDCs in Europe

S.No	NAME OF THE FDC BANNED DRUGS	REASON
1.	Triacelluvax – Combined diptheria,tetanus and acellular pertussis vaccine	Marketed only in Italy. Voluntarly with draw for Marketing Authorisation for TRIACELLUVAX for commercial purposes.

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2.	Neparvis- (sacubitril and valsartan)	A potentially severe side effect, angioedema (rapid swelling of deeper skin tissues as well as the tissues around the throat, causing breathing difficulty),can occur commonly(affecting fewer than1in 100people).
3.	Opdivo and Yervoy-cancer medicines.Active substance (nivolumab and ipilimumab).	The company stated that the with draw was based on the fact that the Agency could not conclude that there was a positive benefit-risk balance for the medicines in the treatment of non-small cell lung cancer that has not been treated previously.

Banned FDCs in US:

S.No	NAMEOFTHEFDCBANNED DRUGS	REASON
1.	Norfloxacin+Metronidazole/ Tinidaze Tinidazole + Loperamide Norfloxacin+Tinidazoe +Dicyclomine Norfloxacin + Ornidazole Ciprofloxacin + Tinidazole Ofloxacin+Metronidazole Ofloxacin+Ornidazole Gatifloxacin+Ornidazole	Combination adds to cost,adverse effects It may increase resistance
2.	Nimesulide+Diclofenac +Nimesulide+Dicyclomine+SimethiconeNimesulide+Paracetamol+Tizanidine	Combining two NSAIDs may increase the side effects of both the NSAIDs
3.	Amoxycillin+Cloxacillin	Amount of each drug is halved,efficacy is Reduced and chances of selecting resistant strains is increased.

Banned FDCs in UK:

S.No	NAMEOFTHEFDCBANNEDDRUGS	REASON
1.	Cefixime+azithromycin	Some superbugs, which are strains of bacteria that have become resistant toantibioticsbecauseoftheuseofirrationalcombinationofantibiotics.
2.	Diclofenac+Paracetamol	It is associated with a small increased risk of cardiovascular side effects and is therefore no longer available over the counter.
3.	Phenylbutazone+Paracetamol /Acetaminophen+Propyphenazone	By taking a small amount of this medicine the intestine get small Punctures and can cause bloodcancer.Thesemedicineshavetakenmorethan15000lives

Banned FDCs in Japan:

S.NO	NAME OF THE FDC BANNED DRUGS	REASON
1.	Paracetamol+Diphenhydramine	It causes tremors,

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	HCl+PhenyephrineHCl+Caffeine	hallucinations, problems in urinating.It has more side effects than benefits.
2.	Dextromethoraphan+Guaifenesin+Pseudophedrine	Intestine get punctures and can cause blood cancer
3.	Diphenhydramine,Ammoniumchloride+Sodiumcitrate	Diphenhydramine—the active ingredient in this allergy med. in Japan, you're limited to ten-milligram capsules.

Banned FDCs in India:

S.No	NAMEOFTHEFDC BANNEDDRUGS	PROHIBITION NO	REASON
1.	Aceclofenac +Paracetamol +Rabeprazol	S.O.705(E)	• PharmacokineticMismatch,may unnecessary exposure to the ingredients and their side effects. • There is no convincing scientific/clinical evidence/justification for the FDC.
2.	Nimesulide+Diclofenac	S.O.706(E)	• Pharmacodynamicaly inappropriate FDC as both similar mechanism of action. • This combination is not as per standard therapeutic guidelines.
3.	Nimesulide+Cetirizine +Caffeine	S.O.707(E)	• The DTAB SubcommitteeconcurredwiththeopinionofSECandopinedthatthesameisapplicableforcetirizinealso • Pharmacokinetic mismatch, may unnecessary exposure to other ingredients and their side effects. • Rationale for including Caffeinein the FDC as provided by the company is not appropriate. • Nimesulide is prohibited for use in children below12 years. • There is no sound scientific/clinical evidence/justification for the FDC.

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			• This combination is not as per Standard therapeutic guidelines.

V. CONCLUSION

Importance and Regulation of Fixed-Dose Combinations (FDCs)

Public Health Significance: The development of Fixed-Dose Combinations (FDCs) is increasingly crucial from a public health perspective. FDCs offer improved convenience, enhanced efficacy through synergistic effects, and better patient compliance. Their growing use highlights the need for effective regulatory frameworks to ensure their safety and efficacy.

Regulatory Approaches:

- **Europe, Japan, and the USA:** Regulatory agencies such as the European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA), and Food and Drug Administration (FDA) manage FDC approvals through rigorous scientific assessments. These frameworks emphasize safety, efficacy, and quality, though the processes can be complex and lengthy.
- **India:** The Central Drugs Standard Control Organization (CDSCO) oversees FDC regulation in India. Despite recent improvements, challenges persist, including issues with irrational and unsafe FDCs. Criticisms have been directed at the regulatory framework and enforcement mechanisms, necessitating greater transparency and coordination.

Challenges and Recommendations: Effective regulation of FDCs depends on a robust regulatory framework, transparent processes, and strict enforcement. Regulatory authorities must balance patient safety with access to innovative treatments. Global collaboration and harmonization among regulatory agencies are essential to ensure consistent quality and effectiveness in FDC regulation.

Overall, enhancing regulatory practices and fostering international cooperation are vital for maintaining high standards in FDC development and ensuring public health benefits.

SOME OF THE ADVANAGES FROM THE ABOVE RESULTS

Here's a compressed summary of the advantages of FDC regulations in Japan, Europe, the USA, and India:

1. **Japan:**
   - **High Standards:** Rigorous safety and efficacy requirements ensure reliable FDCs.
   - **Thorough Trials:** Extensive clinical trials validate product effectiveness.
2. **Europe:**
   - **Unified Framework:** EMA's harmonized regulations streamline approval across the EU.
   - **Flexible Procedures:** Centralized and decentralized options adapt to different needs.
3. **USA:**
   - **Risk-Based Evaluation:** FDA's approach ensures high safety and efficacy through comprehensive assessments.
   - **Therapeutic Superiority:** Demonstrating added benefits over individual components is required.
4. **India:**
   - **Access and Affordability:** CDSCO balances drug availability with safety and affordability.
   - **Bioequivalence:** Ensures consistent therapeutic effects of FDCs.

These regulations collectively ensure that FDCs are safe, effective, and accessible across different markets.

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