Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Fixed dose combination product: A Review

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ARTICLE DETAILS

Article history:
Received on 13 February 2017
Modified on 20 March 2017
Accepted on 23 March 2017

Keywords:
Fixed dose combinations,
Regulation of FDCs products,
India's regulatory framework
.

ABSTRACT

Fixed dose combination (FDC) are combinations of two or more active drugs in single dosage forms. It is the current hot topic of deliberation in the pharmaceutical industry, drug regulatory agency and pharmaceutical trade. It is not so among the doctor who prescribed the medicine or the patients who consume. Basically, it is increases the patients compliance but there are chances of consuming medicines, more than what is required. Reducing treatment complexity can be achieved through the use of single tablet fixed dose combinations of two active pharmaceutical ingredients. FDC's improve patient compliance by reducing the number of pills. Clinical studies revealed that fixed dose combinations had many benefits compared to single entity and separate agents in terms of effects, convenience, compliance and cost. FDCs have become an important alternative to monotherapy in the treatment of diseases as hypertension, diabetes, cancer, tuberculosis, asthma and COPD by offering several advantages including patients compliance, simple dosage schedule, superior efficacy and tolerability, reduced risk of adverse events, cheaper shipment and packaging activities. In conclusion, FDCs had critical issues during evaluation such as safety efficacy, bioavailability and stability.

INTRODUCTION

A combination of two or more actives in a fixed ratio of doses has already been stated by WHO. This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product [1]. Fixed dose combinations (FDC's) product with two or more drugs co-formulated in one dosage form having corresponding mechanism of action and increased therapeutic activity showing new possibilities in the treatment of almost every human disease. Development of FDC's is becoming increasingly important from a public health view point [2]. The most popular and highly profitable FDC's, moving widely in the Indian drug market are analgesics, tonics, antibiotics, cough and cold preparations, multivitamins, iron preparations and antacids.

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The Indian laws are not properly defined to grant marketing approval by central or state drug controlling authorities, hence there is an increase in the number of irrational FDC's in the Indian drug market at an alarming rate. The concept of rational FDC's has not yet penetrated in the minds of physicians; hence evaluation is needed, as large numbers of FDC's are of little importance in terms of effective health care. Thus, it was considered worthwhile to evaluate the pattern of FDC's prescribing in a tertiary care teaching hospital in central India [3].

Regulation of FDC Products

As per the Drugs and Cosmetic Act 1940, any new drug and the authorization to market a drug is to be given by the drug control general of India (DCGI). Before the approval of any drug, the Central drugs standard control organization (CDSCO) undergoes a process with respect to their quality, safety and efficacy. It is an accepted fact that FDC's is treated since a new drug for the reason that by combining two or more drugs. The safety, efficacy and bioavailability of the individual active pharmaceutical ingredients may change. The DCGI monitors the drug

formulations including the combinations of drugs from the angle of safety, effectiveness and rationality [4, 5].

Globally, there is a rising movement to license FDC's products for the market place. Appendix VI of Schedule Y specifies the necessities for authorization for marketing of variety of types of FDC's. FDA guidelines apply to manufacture/import and marketing approval of FDC's as a complete pharmaceutical product considered as new drug as per Rule 122 (E) of Drugs and Cosmetics Act 1940 and their Rules 1945.

A clear explanation with an appropriate therapeutic rationale of the particular combination of active substances proposed will be the basis of approval. It is not always necessary to generate new information. Confirmation may be obtained from the scientific literature subject to its being of sufficient value. In case of FDC's where all the active ingredients are approved individually, if a clinical trial is necessary, confirmatory study to establish efficacy, preferably by similar group comparisons in which the FDC's is compared to its individual substances may be considered when possible a placebo arm may be incorporated.

Comparative clinical trials of the FDC's with reference treatment may be essential, particularly when the therapeutic explanation talks more on the FDC's superiority over a reference treatment. An application for a marketing authorization may comprise entirely original data, entirely data from the literature and both original data and data from the literature (hybrid). For FDC's it is likely that hybrid submissions will be the most ordinary kind. Chemical and pharmaceutical data should be always completely innovative, unless there is enough explanation with literature when partial data can be in-original.

Treasury challan of INR 15,000 if all active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is unapproved or approved for less than one year. However, a challan of only INR 15,000 is required, in case the applicant has already submitted an application along with a challan of INR 50,000 towards any of the single active ingredient approval, which is less than one year old. Any test batch/trial batch of new drugs for test and analysis purpose should be manufactured after obtaining license in Form 29 from the concerned state licensing [2,4].

Advantages of FDC Product

i) Better treatment

1) A reduced pill burden during the intensive phase, with only three or four FDC pills required per day instead of the current 7-8 pills required for the single drug regimen [6]

2) The large number of pills in the current regimen increases the chance that patients will miss taking a specific dose, which can lead to incomplete treatment, or worse, monotherapy with a single drug, increasing the risk of developing drug resistance. This risk can be mitigated with introduction of FDCs, since the essential drugs of the regimen are combined in a single pill [7, 8]

3) Better adherence leads to better treatment outcomes and helps avoid treatment failure and relapses. This is especially true for people with HIV-TB co-infection who are on daily antiretroviral therapy (ART). Poor adherence to either DOTS or ART can lead to drug resistance and in turn lead to poor treatment outcomes for both TB and HIV. In addition, people living with HIV who are on ART are also most in need of daily FDCs (already being implemented for ART), to reduce their over pill burden, simplify treatment literacy and improve levels of adherence [8, 11].

ii) Better case management

1) FDCs simplify the drug supply chain by reducing the number of formulations that must be ordered and distributed, particularly to peripheral parts of the country.

2) FDCs can be cheaper than other regimens because program costs for procurement and distribution are lower. High-volume procurement by the government of India could further reduce costs [6].

iii) Patient compliance

1) FDC may increase patients compliance by taking less tablets on daily basis (e.g. 3-4 tablets/day instead of the 15-16 tablets/day) compared to monotherapy.

2) Medication compliance improved by reducing pill burden of patients [7, 12].

iv) Simple dosage schedule

1) In the treatment of some diseases, such as tuberculosis, 9-16 tables per day may be

required to be used. Patients might experience challenges in remembering and using the drug; it is a condition that can create confusion and put patients in distress

2) With the use of fewer tablets per day, FDA offers a more basic and easy to use schedule [7,8]

v) Greater efficacy compared to monotherapy

Data obtained from the studies with FDC combinations showed that FDC combinations have superior efficacy compared to monotherapy [7, 13, 14].

vi) Reduced risk of adverse events

1) In a study, 5 adverse effects were noticed among 1775 hypertensitive patients. Decrease in incidence of adverse effects with FDC compared to the corresponding free-drug combination was noted, except for one case.

2) A different meta-analysis reports that the adverse effects associated with the use of two drugs combined were less than those associated with those of the two drugs given independently [7,15].

vii) Synergistic effect

1) Fixed dose combinations come together sometimes to create a perfect combination that has a synergistic effect.

2) Paracetamol has quick onset action and Tramadol has prolonged analgesic effect, it has been seen that the fixed dose combination of these two drugs create a synergistic analgesic effect (Figure 1) [7, 17, 18]

viii)Inhibition of microbial resistance

1) Infectious pathogens develop antimicrobial resistance against drugs. Inherently, microbes may be resistant to anti-infective agents or may develop resistant to anti-infective agents.

This resistance can be prevented by different mechanisms generated by different drugs.

2) Fixed dose combinations are more effective to eliminate or slow down antimicrobial resistances compared to monotherapy drugs and free dose combinations [7, 19].

Disadvantages of FDC Product

i) Reduced dosage flexibility

1) Fixed-dose antihypertensive combination products have the disadvantage of lacking the dosing flexibility for its individual components. However, since Amlodipine and Atorvastatin both have several dosage strengths (dose range: 5-10 mg Amlodipine/10-80 mg Atorvastatin), these drugs will not be concerned.

2) Furthermore, fixed-dose combination antihypertensive/dys-lipidemic therapy may not provide a sufficient amount of drug to treat illnesses like angina (in cases where Amlodipine is necessary with doses (higher than 10 mg) that can be found together with hypertension [7].

ii) Drug interactions

1) Drug interactions may occur between active ingredients and excipients which are used in the FDC's according to chemical properties of the substances under the environment (acidic/basic/humidity).

2) Drug interactions are important issues because they may change the therapeutic effect, and may cause the potential incompatibilities and moreover affect the stability.

3) This causes chemical instability between two drugs. In order to prevent this interaction, modified tablet in tablet formulation has been developed [7, 21].

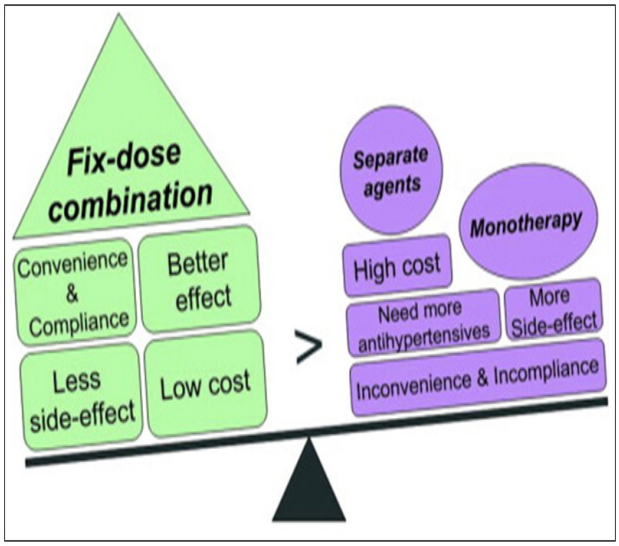

Figure 1: Advantage of FDC as compare to monotherapy

DISCUSSION

Fixed Dose Combination: Rational OR Irrational

Rational drug therapy means the use of the right medicine in right manner like dose, route, frequency of administration, duration of therapy in the right patient at the right cost and right time. However it is staggering to find that over 80,000 formulations are sold in Indian market which includes several FDC's and other single

drug formulations. There has been an alarming increase in irrational FDC's in the recent past and pharmaceutical companies manufacturing these FDCs are luring physicians to prescribe their products even when they are not needed by the patients [1, 16, 20, 22, 23, 39].

Unfortunately many FDC's are being introduced in India are usually irrational. The most pressing concern with irrational FDC's is that they expose patients to unnecessary risk of adverse reactions, for instance, pediatric formulations of Nimesulide and Paracetamol. Nimesulide alone is more antipyretic than Paracetamol, more anti-inflammatory than aspirin, and equivalent in analgesia to any of the NSAIDS alone, so efficacy gains are unlikely with added Paracetamol. However, the patients may be subject to increased hepatotoxic effects due to the combination [22, 24, 25].

In India, a variety of NSAID combinations are available, often as over the counter products. These combinations are an easy way to sell two drugs when one may be needed for the patient [22, 26]. The 'combined' pills are marketed with slogans like 'ibuprofen for pain and paracetamol for fever' and 'ibuprofen for peripheral action and paracetamol for central action'. It is indeed very unfortunate that the medical fraternity in India has fallen prey for the docotor's complacence in terms of extra cost and extra adverse effects. There is no synergism when two drugs acting on the same enzyme are combined. Thus combining two NSAIDs does not and cannot improve the efficacy of treatment. It only adds to the cost of therapy and more importantly to the adverse effects and the 'muscle relaxants' in some of these combinations are of questionable efficacy [27]. Combinations of NSAIDs/analgesics with antispasmodic agents are also available in India [28]. They are not only irrational but also could be dangerous. The antipyretic drug promotes sweating and thereby helps in heat dissipation [29].

Critical Issue During Evaluation of FDC

Safety/Efficacy

Safety is an important sign with regards to the administered of the drug, the efficacy is an important sign with regards to the therapeutic advantage of the FDC compared to monotherapy. Effectiveness and tolerability of fixed dose combination of Amlodipine/Valsartan in treatment of hypertension Egyptian patients were evaluated. The results of this study indicated that single pill combination of Amlodipine/Valsartan effectively reduced BP with high tolerability profile. FDCs of Amlodipine and Valsartan (Exforge) has been shown to be more effective in lowering BP than Amlodipine and Valsartan mono drugs in randomized trials with comparable side effect profile. Amlodipine and Valsartan fixed-dose combination is well tolerated and simplifies antihypertensive regimen enhancing patient adherence and a better BP control compared to monotherapy [30].

The efficacy and safety of Acarbose plus Metformin fixed-dose combination (FDC) compared with Acarbose monotherapy for Type-2 diabetes. The study findings confirmed that Acarbose/Metformin FDC has superior antihyperglycemic efficacy than Acarbose monotherapy [31].

Bioavailability/Bioequivalence

The common approach for the approval of the FDC's is the bioequivalence between the FDC and the mono drugs previously used. The demonstration of bioequivalence between the FDCs and the mono drugs can be very difficult and sometimes, especially insoluble molecules in mono-drugs can complicate the biopharmaceutical and pharmacokinetic behaviors. The BE condition and the acceptance criteria for FDC components are listed in FDA, EMEA and in local regulations [32].

The bioequivalence study was conducted between Triamterene - Hydrochlorothiazide fixed dose generic product and reference product in healthy volunteers. Results obtained from this study showed that the test and reference products were bioequivalent [33]. Bioavailability was evaluated in a study of Amlodipine/Benazepril tablet versus capsule formulation. The results of this bioavailability comparison study in this population of healthy male volunteers suggest that the tablet and capsule formulations of combination Amlodipine-Benazepril are bioequivalent. Both formulations were well tolerated [34].

India's Regulatory Framework

The much amended Drugs and Cosmetics Act 1940 and Drugs and Cosmetics Rules 1945, govern the regulation of drugs. The 1940 law, passed under British colonial rule, placed responsibility for imports on central government with the states being responsible for manufacture, distribution and sale. Following independence in 1947 and subsequent adoption of the constitution, "drugs" became a matter

contained in the "Concurrent List" so that both the National Parliament and the State Legislatures had and have power to make laws in relation to them. In 1952, national rules introduced the concept of a "new drug" along with the requirement for prior central approval for import.

This was followed in 1961 by the requirement for prior central approval for manufacture, along with an obligation on state license applicants to produce evidence that the drug had been approved. FDC's were not specifically mentioned, but they were regarded as new drugs with recorded central approvals for FDC formulations dating (continuously) from 1961. Increased central control of drug regulation has occurred incrementally ever since, whilst the states have retained their licensing powers over the manufacturing and sale of most drugs [35-37].

A 1988 amendment inserted a new Part XA into the national rules entitled "Import or manufacture of new drugs for clinical trials or marketing". Part XA included (and includes) requirements for pre-manufacturing central approval before a state manufacturing license is granted and for license applicants to produce evidence of that approval, whilst expressly including FDC's in the definition of a new drug and setting out specific data submission requirements for FDC's.

After September 1988, FDC's combining drugs for the first time that had been individually approved previously or previously combined FDC's with new claims were expressly included within the definition of a "new drug" under Rule 122E(c). Those FDC's therefore required central approval prior to manufacturing under Rules 122B or 122C, and applicants had to submit evidence to state authorities of that prior approval. This is reflected in the heading of Rule 122D that is "Application for permission to import or manufacture fixed dose combination of drugs.

In 2001, the rules were amended again to impose the legal duty on the CDSCO to be satisfied when approving new drugs for import or manufacture that they are safe and effective. The duty was imposed for FDC's as well, with the amendment further stating that FDC's needed prior approval even though they fell within the definition of new drugs and so were covered as far as the "safe and effective duty" was concerned, whilst the post 1961 provisions and the 1988 amendments covered them as far as the requirement for prior central approval was concerned [32-34].

An amendment in May 2002, inserting Rules 69(6) and 75(6), essentially duplicated the requirement to produce evidence of prior approval of "new drugs" that had been in the rules since 1961 and extended it to require evidence of approval in favour of the applicant.

The 59th report (Section 9.2) noted "some ambiguity" until May 2002. We identified no ambiguity in the rules. Our detailed analysis of the rules leads us to consider that an FDC needed prior central approval for manufacture and the submission to states of evidence of that approval from 1961 if it fell within the three different definitions of a "new drug" applying from 1961–1988, 1988–1999, and 1999 onwards. Rules 69(6) and 75(6) are not relevant to determining that question, but they imposed an additional requirement of producing evidence of approval in favour of the applicant.

Further amendments in 2005 removed references to minimum numbers or ranges of participants and sites in "new drug" clinical trials and gave the CDSCO discretion to override data submission rules. For four years after approval, or after inclusion in the Indian Pharmacopoeia if earlier, companies wanting to market new drugs including FDC's must obtain approval of their own formulation from the CDSCO. After four year, new drugs cease to be deemed "new" drugs, and applications for manufacturing/distribution licences can be made to state licensing authorities without prior CDSCO approval. The numbers of branded products marketed, and the relative contributions to FDC sales (2011–2012) of formulations with and without a record of CDSCO approval ("approved" and "unapproved") and evaluate the impact of the May 2002 amendment to the rules by determining the proportions of new formulations launched on the market before and after 1 May 2002 that had CDSCO approval, the numbers of products arising, and their sales volumes.

Finally, we wished to determine if FDC formulations available in India were approved by United Kingdom (UK) and/or United States of America (US) regulators or included drugs banned, restricted, or unapproved internationally and to apply our findings to make recommendations for rationalising the regulation of, and hence the use of, FDCs in India. FDC Approvals in India using publicly accessible records available from the CDSCO for the period

1961–2013, we collated information on FDC approvals granted annually in each area. The CDSCO listed approvals chronologically in a portable document format (pdf) that included the drugs comprising individual FDC formulations, indication and the date of approval. Relevant information was extractedinto an Excel spreadsheet. We focussed on original FDC being examined. We categorised a formulation as "approved" if the combination of drugs, irrespective of dose amounts or modified release variations was ever recorded as approved by the CDSCO. We categorized a formulation as "unapproved" if it was not included in the list of CDSCO approvals, 1961–2013 (Table 1). We assumed the CDSCO approval records were complete.

Table 1: Regulatory bodies concerned with registration of fixed dose combination products

Approved	This single term is used in the paper to encompass the prior action required by the CDSCO before a state licensing authority can give a license for manufacture/sale/distribution of a new drug. In the Indian legal documents, the terms used are as follows: the CDSCO gives "permission" for import of new drugs, must "approve" manufacture of new drugs, and gives "permission" for the import and manufacture of new drugs, including FDCs.
Unapproved	This term is used in the paper to encompass FDC formulations for which we found no record of CDSCO approval. We assumed CDSCO records were complete.
Drug	A clinically active component in a formulation.
Drugs Technical Advisory Board	The board established under Section 5 of the Drugs and Cosmetics Act 1940 to advise the central and state governments on technical matters arising out of the administration of the act.
Formulation	The drugs combined together to make an FDC product.
Product	The finished FDC as manufactured and named (or branded) by a pharmaceutical company. Multiple companies may choose to manufacture FDC's of the same formulation. FDC's made by different pharmaceutical companies are given brand names to distinguish them from FDCs of the same formulation made by other companies.
State licensing authority	The state-based authority responsible for manufacture, distribution, and sale of drugs. Drugs are required to have a state license before they are marketed.

No information was available publicly on the clinical evidence that was provided to support approvals. State drug authority records of FDC manufacturing/distribution/sale licences were unavailable, but from the list of 294 FDCs banned by the CDSCO in 2007, we identified FDC's in the study categories that had state licenses only.

FDC Approvals in India

Using publicly accessible records available from the CDSCO for the period 1961–2013, we collated information on FDC approvals granted annually in each area. The CDSCO listed approvals chronologically in a portable document format (pdf) that included the drugs comprising individual FDC formulations, indication and the date of approval. Relevant information was extracted into an Excel spreadsheet [2].

We focussed on original formulation approval that is, the first approval granted for the drug combination in the FDC being examined. We categorised a formulation as "approved" if the combination of drugs, irrespective of dose amounts or modified release variations, was ever recorded as approved by the CDSCO. We categorised a formulation as "unapproved" if it was not included in the list of CDSCO approvals 1961–2013 We assumed the CDSCO approval records were complete. No information was available publicly on the clinical evidence that was provided to support approvals.

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FDC Appovals in the UK AND US

To determine approvals in the UK and US, we searched the Medicines and Healthcare Products. The FDA index (the Orange Book) lists all approved FDC's and single drug formulations (SDF's) alphabetically by generic name.

The MHRA publishes no index of generic name FDC approvals and its list of approvals does not include medicines licensed centrally by the European Medicines Agency, so to minimize the risk of overlooking FDC's approved for use in the UK we also examined listings in the British National Formulary and in the Monthly Index of Medical Specialties (MIMS) [35,40].

FDC Approval in Europe

There are two regulatory steps to go through before a drug is approved to be marketed in the European Union. These two steps are clinical trial application and marketing authorization application. There are 28 member states in the European Union (as of July, 2013); Clinical Trial Applications are approved at the member state level, whereas marketing authorization applications are approved at both the member state and centralized levels

Centralized procedure

The centralized procedure is one which allows applicants to obtain a marketing authorization that is valid throughout the EU.

Timeline: EMA opinion issued within 210 days, and submitted to European Commission for final approval. Centralized process is compulsory for: Those medicines which are derived from any biotechnology processes, such as genetic engineering. Those medicines which are intended for the treatment of cancer, HIV/AIDS, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions. Medicines officially designated 'Orphan medicines' (medicines used for rare diseases).

Mutual Recognition Procedure

The Mutual Recognition procedure allows applicants to obtain a marketing authorization in the concerned member states (CMS) other than the Reference member state (RMS), where the drug is previously approved. Applicant submits identical dossier to all EU member states in which they want marketing authorization, including required information. As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "RMS"), it notifies this decision to other Member States (which then become the "CMS"), to whom applications have also been submitted. RMS issues a report to other states on its own findings. Generic industry is the major user of this type of drug approval procedure. This process may consume a time period of 390 days [41, 42].

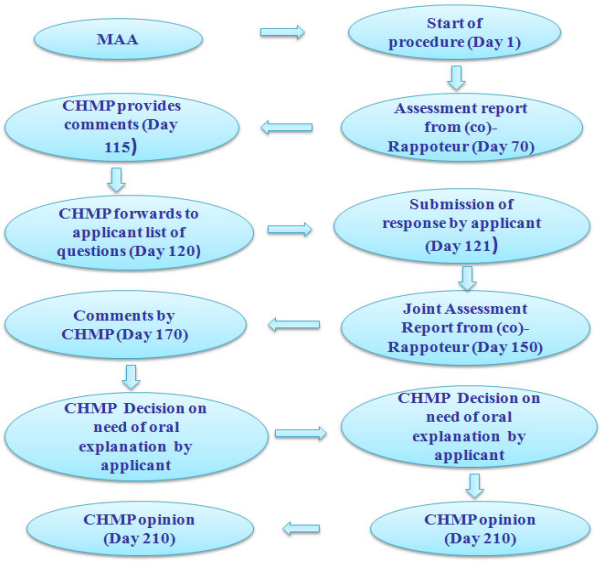
Nationalized Procedure

The Nationalized procedure is one which allows applicants to obtain a marketing authorization in one member state only. In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State. New active substances which are not mandatory under Centralized procedure can obtain marketing authorization under this procedure. Timeline for this procedure is 210 Days.

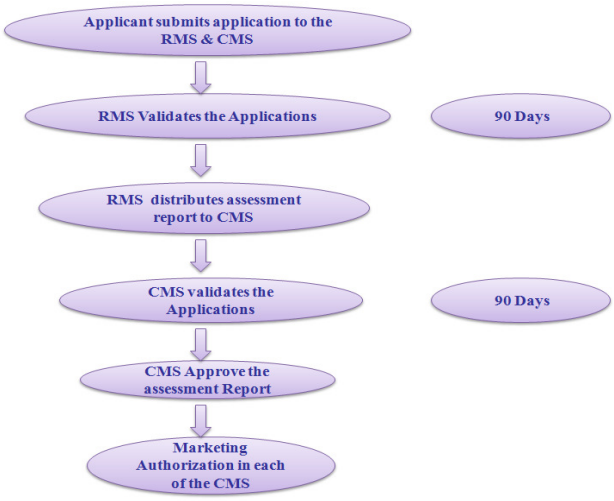
Decentralized procedure

Using this procedure, companies may apply for authorization simultaneously in more than one EU country for products that have not yet been authorized in any EU country and essentially do not fall within the centralized procedure's essential drugs list.

Based on the assessment report which is prepared by the RMS & any comments made by the CMS, marketing authorization should be granted in accordance with the decision taken by the RMS & CMS in this decentralized procedure [41, 42]. Generally used for those products that has not yet received any authorization in an EU country (Time: 210 days).



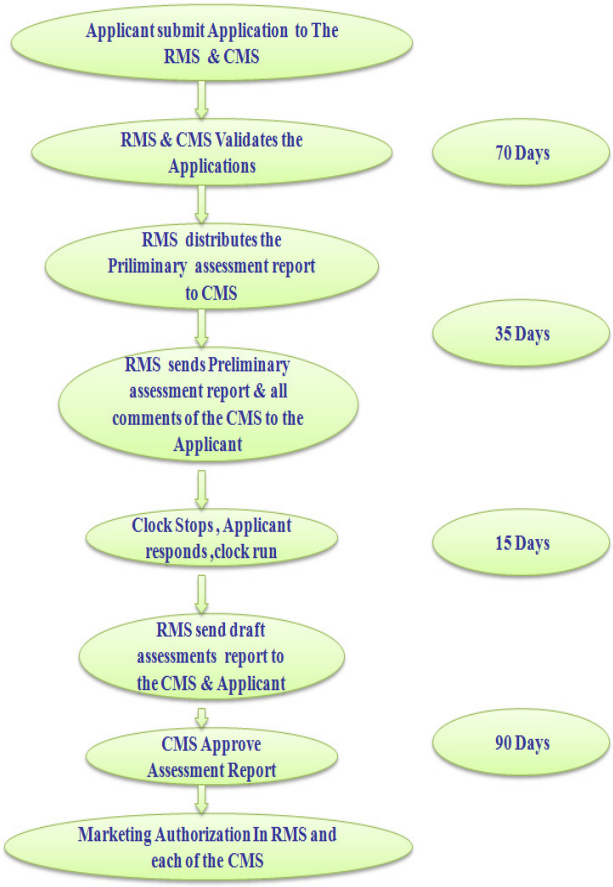
Flow chart 1: Decentralized Procedure



Flow chart 2: Mutual Recognition Procedure

Table 2: Principle differences between US, EU and India

Requirements	US	EU	INDIA
Agency	One Agency USFDA	Multiple Agencies • EMEA • CHMP • National Health Agencies	One Agency DCGI
Registration Process	One Registration Process	Multiple Registration Process • Centralized (European Community) • Decentralized (At least 2 member states) • Mutual Recognition (At least 2 member states) • National (1 member) state)	One Registration Process
TSE/BSE Study data	TSE/BSE Study data not required	TSE/BSE Study data required	TSE/BSE Study data required
Braille code	Braille code is not required on labelling	Braille code is required on labeling	Braille code is not required on labeling
Post-approval changes	Post-approval changes in the approved drug: • Minor changes • Moderate changes • Major changes	Post-variation in the approved drug: • Type IA Variation • Type IB Variation • Type II Variation	Post approval changes: Major quality changes Moderate quality changes



Flow chart 3: Decentralized Procedure

Table 3: Administrative Requirements

Requirements	US	EU	INDIA
Application	ANDA / NDA	MAA	MAA
Debarment classification	Required	Not Required	Not Required
Number of copies	3	1	1
Approval Timeline	~18 Months	~12 Months	12 - 18 Months
Fees	Under $2 million- NDA Application $51,520 – ANDA Application	National fee (including hybrid applications): £103,059 Decentralised procedure where UK is CMS: £99,507	50,000 INR
Presentation	eCTD & Paper	eCTD	Paper

Success Factors for FDC Products

A) Formulation Development challenges

A variety of issues potentially exist when combining two or more molecule. It is not as easy as combining two or more molecule in a tablet press or capsule. It is very important to understand the mechanism of action, chemistry of each component as well as drug substance preformulation characteristics also very important. Below is the just few formulation consideration [22].

- Release profile differences
- Incompatibility
- Delivery Challenges
- Particle size
- Regulatory requirement

B) Patent Feasibility

Getting patent is not as easy as submitting a concept that appears unique. The criteria for that product should be innovative and show functionality. Patent are granted on following criteria;

- Must be novel i.e. not publically known.
- Must be inventive i.e. not obvious over what was already known. It should be noted that the obviousness hurdle is getting higher each year. If one's have an idea or unique concept, chances are so has somebody else. It is a good idea to research whether someone has gone down that road prior. The more successful combination products typically focus on unmet medical needs. To strengthen any patent, build innovation into the formulation .Generic companies are getting better at circumventing formulation patents [22].

C) Pricing & Reimbursement

- Premium valuation higher than mono-therapy is changing into more difficult. Raised unit sales should be the primary goal. Reimbursement isn't generally a problem if combination product isn't premium priced.
- Reimbursement at premium valuation can only hold if there's a transparent useful outcome [22]

D) Physician Considerations

- Many physicians prefer to select relative dosing of combination components on the basis of individual patient. Any need to titrate the drug dose can add complications. Identifying source of side effects can be difficult [22].
- Patients may potentially be exposed to drugs they do not really need conceptually, medication management & compliance should improve with patients. However, little evidence exists regarding compliance improvement [22].

CONCLUSION

This critical review provides information regarding the fixed dose combination and fixed dose combination therapy. The use of FDC therapy has been widely accepted in recent years due to its convenience and advantage they provide for treatments. Instead of taking two or more drugs, the use of a single medication has eased the patient's life as well as physicians in prescribing drugs.

The popularity of FDC's is increasing rapidly, particularly when more than one disease is found in a patient. Patients have already seen the benefit of the combination products in areas such as oncology, cardiology, neurological, metabolic disorders, respiratory and cancer. Patient cannot have access to rational FDC's and they are not always prescribed by the prescribers. Many doctors were ignorant about the essential drugs. Physicians and regulators should get alerted in time and regulatory actions or government laws should be made mandatory.

On the other side, irrational FDC's may impose unnecessary financial burden on consumers. The time has come for all practitioners and consumers to raise this matter vociferously through all possible ways. Drug regulatory bodies should take urgent action to stop the free flow of irrational FDC's. It offers a simple and feasible dose schedules for some patients, such as tuberculosis, who are required to use many tablets during the day. In addition to these advantages, the lack of flexibility in dosage, side effects due to one of the components in the content of the drug and the interactions with other drugs have caused restrictions on the administration of the drug.

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