CURRENT PRESCRIBING TRENDS AND RATIONALITY OF FIXED DOSE COMBINATIONS IN A SOUTH INDIAN MULTI SPECIALTY HOSPITAL - AN OBSERVATIONAL STUDY

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OCTOBER-2021

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Institutional Ethical Committee meeting was conducted at our campus and the Project has been approved and can be carried out in the Topic: **"CURRENT PRESCRIBING TRENDS AND RATIONALITY OF FIXED DOSE COMBINATIONS IN A SOUTH INDIAN MULTI SPECIALITY HOSPITAL -AN OBSERVATIONAL STUDY "**

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Dedicated To

Our Beloved Parents

&

Our Friends

ABBREVIATION

FDC	FIXED DOSE COMBINATION
API	ACTIVE PHARMACEUTICAL INGREDIENTS
ADR	ADVERSE DRUG REACTION
DCGI	DRUG CONTROL GENERAL OF INDIA
CDSCO	CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
FDA	FOOD AND DRUG ADMINISTRATION
ART	ANTIRETROVIRAL THERAPY
HIV	HUMAN IMMUNO VIRUS
NSAID	NON STEROIDAL ANTI INFLAMMATORY DISEASE
CMS	CONCERNED MEMBER STATES
WHO	WORLD HEALTH ORGANISATION
ACE	ANGIOTENSIN CONVERTING ENZYME
T2DM	TYPE 2 DIABETES MELLITUS
MDR	MULTI DRUG RESISTANCE

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1.INTRODUCTION

Fixed dose drug combinations (FDCs) are defined by the World Health Organization (WHO) as a combination of two or more active ingredients in a fixed ratio of doses and in a single dosage form. Drugs from different pharmacological groups with complementary mechanism of action should be combined in FDCs. When they are combined in a single formulation, the safety, efficacy and bioavailability profiles of the established drugs change, and hence, FDCs are treated as new drugs (Rayasam S P et al., 2013).Physicians prescribe a number of FDCs today in which majority of them are irrational. FDCs are widely accepted when it offers justifiable advantages over the products with single active pharmaceutical ingredients (API) (Prajapati K et al.,2016). Advantages of FDCs include better efficacy, reduced adverse drug reaction (ADR), provide broader spectrum of antibacterial activity, reduced complications, ease of administration and reduced polypharmacy. The use of combination drugs with fixed dose helps exhibit its effects with fewer pills or dose, thus improving the patient compliance. It may also reduce the cost and offer the poor patient's a lower overall health care cost. The drugs in combination may provide a synergistic or an additive effect.

Regulation of FDC Products

As per the Drugs and Cosmetic Act 1940, any new drug and the authorization to market 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 .

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. (Rayasam S P et al., 2013).

Advantages of FDC Product

Better treatment

- 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 (Rayasam S P et al., 2013).
- The large number of pills in the current regimen increases the chance that patient's 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 (S.N. Gohel et al., 2015).
- 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 "

Better case management

- 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.

- 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 (Rayasam S P et al., 2013).

Patient compliance

- FDC may increase patient's compliance by taking less tablets on daily basis (e.g. 3-4 tablets/day instead of the 15-16 tablets/day) compared to monotherapy.
- Medication compliance improved by reducing pill burden of patient's

Simple dosage schedule

1. In the treatment of some diseases, such as tuberculosis, 9-16 tables per day may be required to be used. Patient's might experience challenges in remembering and using the drug; it is a condition that can create confusion and put patient's in distress.
2. With the use of fewer tablets per day, FDA offers a more basic and easy to use schedule. (S.N. Gohel et al., 2015).

Greater efficacy compared to monotherapy

Data obtained from the studies with FDC combinations showed that FDC combinations have superior efficacy compared to monotherapy(S.N. Gohel et al., 2015).

Reduced risk of adverse events

1. In a study, 5 adverse effects were noticed among 1775 hypertensitive patient's . 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 (S.N. Gohel et al., 2015, wang J.S et al.,2013).

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) (S.N. Gohel et al., 2015, Guptha A. et al., 20120).

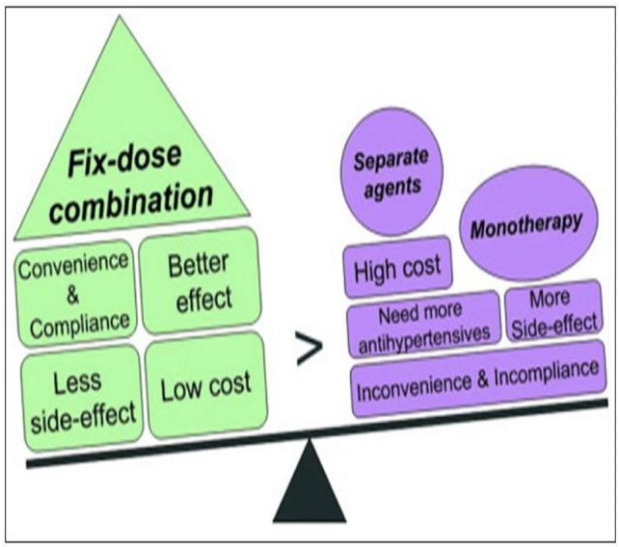


Figure: Advantage of FDC as compare to monotherapy

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. (S.N. Gohel et al., 2015).

Disadvantages of FDC Product

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-1ipidemic 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 (S.N. Gohel et al., 2015).

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 (S.N. Gohel et al., 2015).

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 patient's (Dononue J. et al ., 2013)

Unfortunately, many FDC's are being introduced in India are usually irrational. The most pressing concern with irrational FDC's is that they expose patient's to unnecessary risk of adverse reactions, for instance, paediatric 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 patient's may be subject to increased hepatotoxic effects due to the combination(Sarwar M.S et al., 2012)

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 (Sarwar M.S et al., 2012) .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 doctor's compliance 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 (Burke A. et al., 2006). Combinations of NSAIDs/analgesics with antispasmodic agents are also available in India (Rayasam S P et al., 2013). They are not only irrational but also could be dangerous. The antipyretic drug promotes sweating and thereby helps in heat dissipation.

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 patient's 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 (Prajapati K et al.,2016).

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 (Mitra A et al ., 2012).

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 .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 (Gupta V. et al ., 2013)

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 (McGettigan et al.,2015)

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 1998, 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 (Mithra A et al., 2012).

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 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. We assumed the CDSCO approval records were complete.

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 (Rayasam S P et al., 2013).

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.

State drug authority records of FDC manufacturing/distribution/sale licences were unavailable, but from the list of 294 FDC's banned by the CDSCO in 2007, we identified FDCs in the study categories that had state licenses only 9Kafrawy N E et al., 2014, Mitra A et al.,2012).

FDC Approvals 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) (Kafrawy N E et al., 2014).

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(Gupta V et al., 2013 , Prajapati V etal., 2014).

Nationalized Procedure

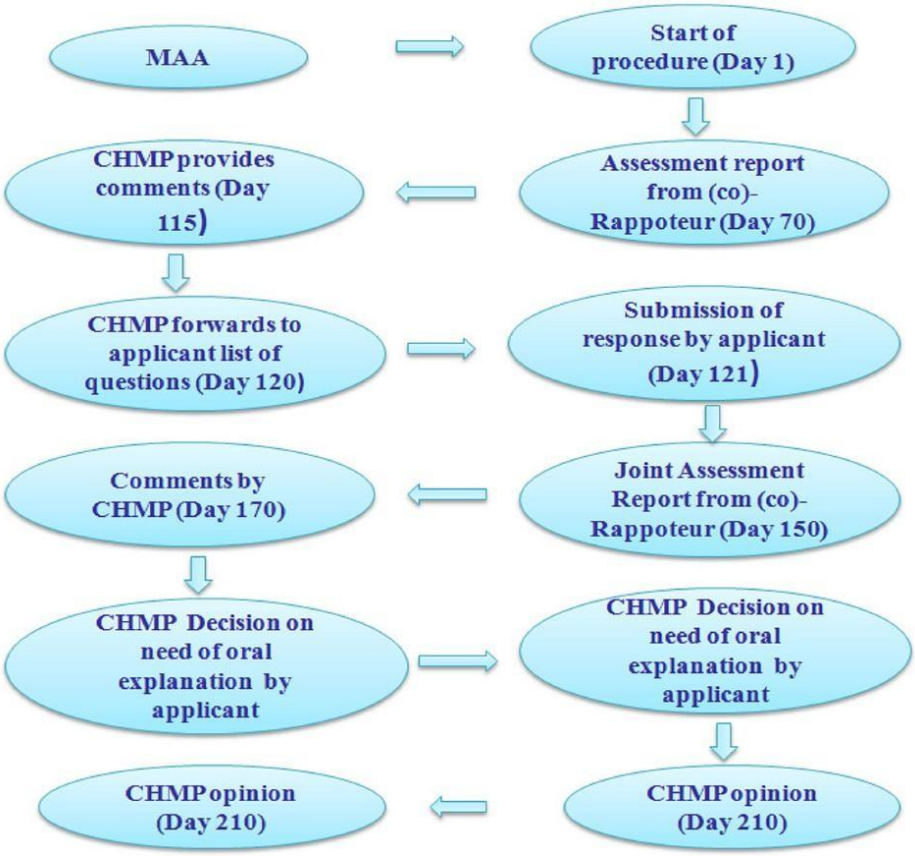
The Nationalized procedure is one which allows applicants to obtain a marketing authorization in one member state only. In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State. New active substances which are not mandatory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

Decentralized procedure

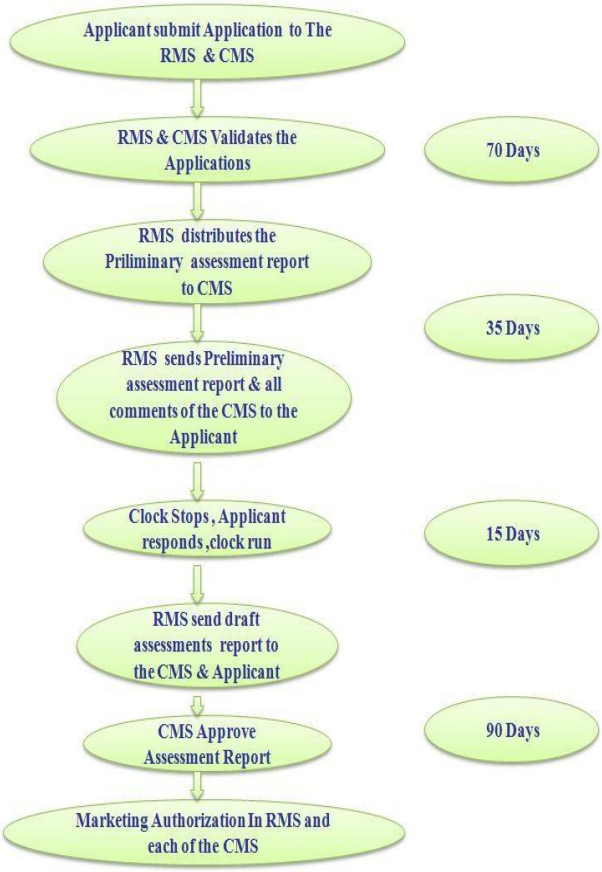
Using this procedure, companies may apply for authorization simultaneously in more than one EU country for products that have not yet been authorized in any EU country and essentially do not fall within the centralized procedure's essential drugs list.

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 (Gupta V et al., 2013, Prajapati V et al.,

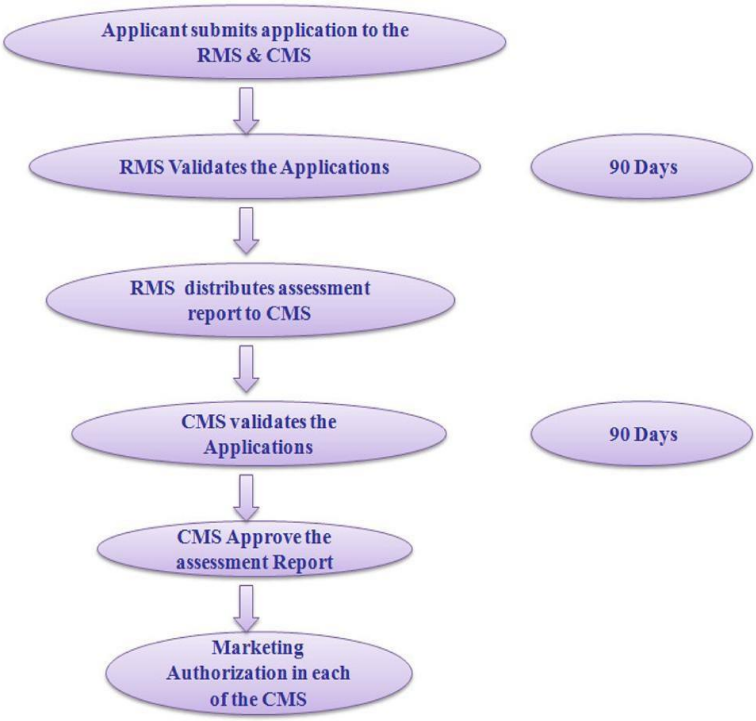
2014). Generally used for those products that has not yet received any authorization in an EU country (Time: 210 days).



Flow chart: Decentralized Procedure



Flow chart: Decentralized Procedure



Flow chart: Mutual Recognition Procedure

Table: 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

Formulation Development challenges

A variety of issuespotentially 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 pre-formulation characteristics also very important. Below is the just few formulations consideration.

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

- Regulatory requirement

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 [Sarwar M S et al., 2012].

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 (Sarwar M S et al., 2012).

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 (Sarwar M S et al., 2012)..

- Patient's may potentially be exposed to drugs they do not really need conceptually; medication management & compliance should improve with patient's . However, little evidence exists regarding compliance improvement (Sarwar M S et al., 2012).

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. Patient's 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 patient's , 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.

Fixed dose drug combinations (FDCs): rational or irrational: a view point [43-53]

Combination products, also known as fixed dose drug combinations (FDCs), are combinations of two or more active drugs in a single dosage form. The Food and Drug Administration, USA defines a combination product as 'a product composed of any combination of a drug and a

device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product. It is widely accepted that most drugs should be formulated as single compounds. Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance.FDCs are highly popular in the Indian pharmaceutical market and have been particularly flourishing in the last few years.

The rationality of FDCs should be based on certain aspects such as:

- The drugs in the combination should act by different mechanisms.
- The pharmacokinetics must not be widely different.
- The combination should not have supra-additive toxicity of the ingredients.

Most FDCs have the following demerits:

- Dosage alteration of one drug is not possible without alteration of the other drug.
- Differing pharmacokinetics of constituent drugs pose the problem of frequency of administration of the formulation.
- By simple logic there are increased chances of adverse drug effects and drug interactions compared with both drugs given individually.

The recent 14th model list of essential drugs prepared by the WHO (March 2005) includes 312 formulation of which 18 are fixed dose drug combinations.

The World Health Organization's (WHO) Model list of Essential Drugs provides examples of some rational FDCs such as:

- Sulfamethoxazole + Trimethoprim
- Antitubercular FDCs like Rifampicin + Isoniazid, Isoniazid + Ethambutol, etc
- Anti-parkinsonism FDCs like levodopa + carbidopa

Unfortunately, many FDCs being introduced in India are usually irrational. The most pressing concern with irrational FDCs is that they expose patient's to unnecessary risk of adverse drug reactions, for instance, paediatric formulations of Nimesulide + Paracetamol. Nimesulide alone is more antipyretic than paracetamol, more anti-inflammatory than aspirin, and equivalent in analgesia to any of the NSAIDS alone (S P Rayasam et al.,2013), so efficacy gains are unlikely with added paracetamol. However, the patient's may be subject to increased hepatotoxic effects from the combination. FDCs of diclofenac + serratopeptidase do not offer any particular advantage over the individual drugs despite the claim that serratopeptidase promotes more rapid resolution of inflammation. On the other hand, the patient is exposed to greater risk of gastrointestinal (GI) irritation and serious bleeding from unsuspected peptic ulceration. FDCs of quinolones and nitroimidazoles (e.g., norfloxacin + metronidazole, ciprofloxacin + tinidazole, ofloxacin + ornidazole) have not been recommended in any standard books, but continue to be heavily prescribed drugs in GI infections, pelvic inflammatory disease, dental infection, etc., to cover up for diagnostic imprecision and the lack of access to laboratory facilities. Such injudicious use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, which is a matter of serious concern to the health care situation in our resource poor country. A glaring example is the emergence of ciprofloxacin-resistant Salmonella typhi strains which have made treatment of typhoid fever a difficult and expensive proposition in India today.

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 (or even none) may be needed for the patient. 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 to such gimmicks. The gullible patient then has to pay for the doctor'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.

Combinations of NSAIDS/analgesics with antispasmodic agents are also available in India. They are not only irrational but also could be dangerous. The antipyretic drug promotes sweating and thereby helps in heat dissipation. On the other hand, the anticholinergic antispasmodic drug inhibits sweating. Combining these two can result in dangerous elevation of the body temperature. Some such fixed drug combinations are now banned in India.

Over the years the Indian Drug Control Authority has issued banned notifications on many FDCs like analgin + pitofenone, vitamins B1 + B6 + B12, cyproheptadine + lysine, etc. But are these measures sufficient? Obviously not, since these notifications have not deterred manufacturers from coming out with new irrational FDCs. At this crucial juncture, when the global community, represented by WHO, is making an all-out effort to propagate the concept of essential drugs amongst consumers throughout the world, our official stance could be viewed as too meager. India, as the world's second most populous country, should demand a more rational approach and not pay mere lip service to the global campaign.

Irrational FDCs also impose unnecessary financial burden on consumers. Medical practitioners who patronize such combinations could be the centre of controversy when

subjected to litigation in consumer forums, as these combinations do not find mention in standard text or reference books and reputed medical journals. Pharmaceutical manufacturers, however, continue to reap the benefits of huge sales, and therefore continue to promote combinations with vigour. The time has come for all practitioners and consumers to raise this matter vociferously through all possible avenues. Drug regulatory bodies should take urgent action to mitigate the free flow of irrational FDCs.

Positive clinical and economic (general) considerations associated with FDCs

Clinical benefits associated with FDCs (general)

- Simplifies the treatment schedule – which can be particularly important in LMICs where there are low literacy levels as seen in a number of sub-Saharan African countries
- Easier to prescribe
- Improved adherence with reduced pill burden
- Minimal frequency of medicine consumption and reduced chances of patient's missing doses
- Potential to attain clinical goals more rapidly through complimentary additive effects of the components and/or reduced titration times
- Potential for increased tolerability and/or fewer side-effects through the combination of synergistic medicines
- Reduced chances of stockouts with FDCs versus the components especially for FDCs containing multiple medicines; consequently, potentially improving clinical outcomes

Economic benefits (general) associated with FDCs

- Potential for reduced overall costs enhanced by synergism with lower doses – potential for lower costs than the components enhanced if FDCs are produced and procured at low cost aided by mass approaches to production, packaging, and distribution
- Reduced space for storage and distribution/potentially reduced logistical costs
- Potential for improved shelf life
- Now seeing in countries that prices of FDCs cannot be higher than the costs of the individual components (e.g. Slovenia) and may even be lower (e.g. India and Zambia)

Positive clinical considerations with FDCs across disease areas -Benefits of FDCs

Cardiovascular diseases including hypertension

- Improved dose frequency and ease of administration help improve adherence especially where patient's are on multiple medicines due to existing co-morbidities – potentially improving disease management
- Potential for improved effectiveness by combining different treatments with different mechanisms of action, e.g. different lipid-lowering treatments
- One component of an FDC may offset the side-effects seen with other components, e.g. ACE inhibitors offsetting one of the major side effects associated with calcium channel blockers
- Potential for minimal adverse effects alongside improvement in disease management
- Improved long-term adherence through reduced pill burden especially important among aging populations, e.g. European LMICs

Type 2 Diabetes Mellitus (T2DM)

- Potential for improved adherence through reduced pill burden – especially important in T2DM patient's with multiple comorbidities to enhance adherence rates
- Improved disease control for patient's with T2DM as well as potentially reducing complications through using medicines with different mechanisms of action
- In some countries, helps increase the prescribing of metformin where this is a concern and SUs available in combination with metformin

Respiratory diseases

- FDCs containing ICS/LABAs are seen as a standard of care for the maintenance of patient's with asthma
- Improved acceptance of FDCs versus separate inhalers helped by easier administration
- Reduced doses of steroids where there are concerns with continued high doses of steroids for maintenance among patient's with asthma
- FDCs seen to improve the quality of life of patient's with asthma through improved adherence and better maintenance of disease targets

Pain

- Improved potential for pain management with FDCs with different mechanisms of action where concerns with abuse or increased side-effects if the dose of one component is increased to manage the pain
- Multiple mechanisms for a broader effect

Malaria

- Improved effectiveness and treatment success

- Improved adherence to prescribed medicines enhanced by the potential for shortened duration of treatment
- Potential for decreased resistance using medicines with different mechanisms of action
- Potential for reduced costs

Tuberculosis (TB)

- FDCs may help prevent the emergence of resistant strains especially given the length and complexity of the treatment regimens involved
- Increased effectiveness against resistant cases with medicines with different mechanisms of action
- Reduces the incidence of MDR-TB
- Synergism at lower doses
- Complex treatment regimen eased by FDCs thereby enhancing completion rates
- Dispersible FDCs for children easing administration

Human immunodeficiency virus (HIV)

- FDCs containing medicines with different mechanisms of action typically improves treatment outcomes
- Synergism at lower doses
- FDCs may help prevent the emergence of resistant strains
- Increased effectiveness against resistant cases
- Combining tablets simplifies treatment regimens and standardizes doses prescribed aiding subsequent quality of care
- Patient's are unable to default on specific medicines believed to be causing side-effects such as dizziness and drowsiness seen with efavirenz

General concerns regarding FDC

Clinical concerns associated with FDCs (general)

- Reduces the ability to titrate individual doses to the specific needs of patient's
- Potential for overtreatment if physicians and patient's are not fully aware of the constituents of FDCs – especially important if patient's are switched to different FDCs
- FDCs can increase polypharmacy especially in patient's with chronic NCDs
- Issues of pharmacokinetics in some FDCs including issues of dissolution, absorption and drug:drug interactions
- Missing doses of an FDC has a greater impact than missing doses of one of the medicines in the FDC
- Challenging to ascertain responsible medicine for ADRs – especially important for pharmacovigilance

Economic concerns (general) associated with FDCs

- Potentially appreciably higher prices for the FDC versus the cost of the components combined
- Typically only available as 'branded' medicines in some countries and consequently only available in private pharmacies rather than public facilities and not in rural areas, e.g. Cameroon

Clinical concerns regarding FDCs across disease areas - Concerns with FDCs

Cardio Vascular (CV) diseases including hypertension

- Reduces the ability to tailor treatment to individual patient's especially where adverse effects are seen with the prescribed FDC
- More limited options with FDCs versus individual components
- More difficult to adjust doses when needed potentially enhancing treatment inertia

- Potential for doubling doses of medicines if patient's and prescribers are not fully aware of the constituents of prescribed FDCs
- Clinical rationality of a number of CV FDCs with the potential for inadequate dosing and increasing costs
- Concerns with the bioequivalence and pharmacokinetics of some FDCs for CV diseases

Type 2 Diabetes Mellitus (T2DM)

- More difficult to adjust doses thereby potentially reducing the ability to tailor treatment to individual patient's
- More limited options with FDCs versus individual components
- Reduced positive effect of metformin on CV events with reduced doses of metformin or with metformin/sulfonyl urea combinations
- Potential for doubling doses of medicines if patient's and prescribers are not fully aware of the constituents of prescribed FDCs
- Clinical rationality of a number of FDCs, e.g. metformin FDCs in India
- FDCs enhance the potential for polypharmacy, e.g. in Slovenia many patient's with T2DM are typically on 4 or more INN medicines which was not often seen before the availability of FDCs

Respiratory diseases

- Reduces the potential for effective management especially where there are concerns with the doses of steroids administered – as a result, potential for over medication with steroids
- Patient's may need to use different inhaler devices with different FDCs impacting on adherence in practice

- Increasing concerns with prescribing of LABA/ICS combinations in patient's with COPD unless asthma-like symptoms

Pain

- Reduces the ability to tailor treatment to individual patient's
- More difficult to adjust doses
- Potential for substance misuse if currently taking FDCs due to the subjective nature of pain
- Limited clinical justification for FDCs to treat pain among some of the coauthors
- Potential to enhance irrational prescribing

Malaria

- Potential concerns with tolerance to mefloquine FDCs
- Appreciable number of unapproved FDCs in some LMICs
- Concerns with the pharmacokinetic profile of some FDCs for malaria impacting on their effectiveness and safety
- Potential loss of effectiveness
- Potential development of drug resistance to one or more of the components leading to loss of therapeutic options

Tuberculosis (TB)

- Difficult to desensitize patient's in the event of adverse effects
- Potential for increased adverse events
- Some constituents of FDCs may cause more adverse effects than the originators
- Potential quality issues when medicines are combined especially with rifampicin in FDCs for TB – consequently vigilance is needed to monitor the quality of rifampicin

as a key component of antimalarial FDCs given concerns with certain rifampicin FDCs in countries such as South Africa

- Potential loss of effectiveness
- Potential development of drug resistance to one or more of the components leading to loss of therapeutic options
- The interaction between efavirenz as well as lopinavir, dolutegravir, raltegravir with bedaquiline is a problem for patient's with HIV who also have MDR-TB (especially in sub-Saharan Africa) – necessitating a switch to twice daily nevirapine with separate companion tablets – antiretroviral FDCs without bedaquiline drug interactions are strongly recommended in these patient's

Human immunodeficiency virus (HIV)

- Difficult to desensitize patient's in the event of adverse effects, with the potential for increased adverse events with FDCs
- Some constituents of FDCs may cause more adverse effects than the originators necessitating careful monitoring of patient's
- Potential loss of effectiveness over time
- Potential development of drug resistance to one or more of the components leading to loss of therapeutic options
- Currently, no liquid formulation FDCs are available for pediatric patient's
- Imperative to educate patient's that FDCs cannot be crushed or dissolved to improve swallowing as bioequivalence will be compromised
- Supply chain integrity is imperative to ensure a continuous supply of ARV FDCs for patient's with interruptions in supply associated with sub-clinical outcomes

Potential initiatives that can be undertaken by key stakeholder groups to enhance the availability and prescribing of valued FDCs.

Clinical and other considerations

- Emphasize the importance of adherence to treatments especially for patient's with chronic NCDs and how valued FDCs can help with this. Concurrent with this, improve prescriber education about the benefits of valued FDCs starting in medical school and continuing post qualification – similarly for pharmacists who are increasingly involved with patient education regarding their medicines and the importance of adherence to prescribed doses
- Possibly linked to this, the development of quality prescribing indicators potentially linked with financial rewards
- Pharmaceutical companies to provide robust clinical trial data demonstrating improved outcomes and adherence with FDCs versus the components separately to aid listing in country/region reimbursement list/EML (such data when available can be incorporated into robust health technology assessments of new FDCs)
- Investigate further the clinically meaningful benefits of the polypill especially for sub-Saharan Africa given the appreciable increase in morbidity and mortality due to CV diseases in recent years in these countries
- Robustly considering any potential drug:drug interactions or increased adverse effects in patient's with HIV subsequently developing chronic NCDs (increasingly happening in sub-Saharan Africa) and prescribed FDCs – especially as this co-morbid population is likely to experience challenges with medication adherence/polypharmacy
- The process from transitioning from individual medicines to FDCs should be carefully managed in terms of supply chain management (where problems currently exist) to

facilitate procurement at a central level (and hence procurement at lower prices) and subsequent distribution

- Appropriate patient counseling also needs to take place to optimize the process – with intensive adherence counseling still needed especially among patient's with limited education. In view of this, if appropriate create policies that enhance capacity within health-care systems that help spread correct information and awareness regarding the value and effectiveness of pertinent FDCs as well as use patient organizations where these exist to spread key messages – this can include instigating educational activities among physicians and pharmacists in medical and pharmacy schools and post-qualification
- Accelerating the registration/pricing procedures for valued FDCs in countries where this is a concern, e.g. Sudan. This can be addressed through the provision of scientifically sound guidelines and robust data supporting their registration as well as a review of reimbursement/pricing procedures where there are concerns
- More flexible approaches to private pharmacies regarding the availability of FDCs especially in rural areas where this is a concern, e.g. Cameroon

Economic

- Realistic pricing expectations and considerations especially where there are high patient co-payments or strict pricing regulations, e.g. Estonia, to help overcome concerns with the over-pricing of FDCs and enhance their chances of being reimbursed/listed in national/regional EMLs – typically initially robust health technology assessments using cost minimization approaches are needed among LMICs to enhance their listing in national EMLs (progressing to costeffectiveness analyses as sophistication levels grow)

- Addressing issues of affordability and access where these exist – including reducing additional patient co-payments for the FDC versus multiple tablets of the same medicines where these exist especially for valued FDCs, e.g. Bulgaria and Poland
- Concurrent with this, promoting local pharmaceutical company participation in the manufacturing of FDCs to agreed quality standards through incentives and other mechanisms to help address supply chain and affordability/access issues where these exist

Potential initiatives that can be undertaken by key stakeholder groups to reduce or negate the availability of FDCs where concerns.

Clinical

- The development of public/private partnerships to help standardize treatment approaches including the prescribing of FDCs
- Provision of robust health technology assessments to support listing/funding of FDCs in LMICs – especially for more elderly patient's with high pill burdens. This includes robust cost-effectiveness analyses across LMICs demonstrating their value versus the prescribing of multiple medicines for the same patient population
- Concomitant with this – greater focus on issues of potential polypharmacy with FDCs especially in elderly patient's with multiple co-morbidities
- Only register FDCs of proven clinical value, enforced through tighter regulations – especially important in countries with existing high rates of irrational FDCs, e.g. India – although changing – and to prevent the future availability of FDCs where concerns
- Improved education of undergraduates and physicians where concerns with irrational FDCs, e.g. India. This should be continued with activities after qualification including in-service training/continual professional development to enhance adherence rates

among patient's to prescribed FDCs given ongoing concerns with long-term adherence to medicines especially in patient's with chronic asymptomatic conditions

- Improve pharmacovigilance activities especially for FDCs where there are safety as well as drug:drug interaction concerns
- Greater interaction and empowerment of national patient organizations to enhance the appropriate use of valued FDCs and limit the prescribing/use of FDCs where there are clinical and other concerns
- Enforce legislation and monitor activities to reduce or negate non-prescription sales of FDCs especially where concerns with their rationality

Economic

- Tougher hurdles for pricing/reimbursement considerations to reduce reimbursement/listing of FDCs of limited clinical value as well as unjustifiably higher prices than the components combined.

What is an Essential Medicines List?

As per the WHO, Essential Medicines are those that satisfy the priority health care needs of the population. The list is made with consideration to disease prevalence, efficacy, safety and comparative cost-effectiveness of the medicines. Such medicines are intended to be available in adequate amounts, in appropriate dosage forms and strengths with assured quality. They should be available in such a way that an individual or community can afford.

Drawing an essential medicines list (EML) is expected to result in better quality of medical care, better management of medicines and cost-effective use of health care resources. This is especially important for a resource limited country like India. The list of essential medicines is intended to have a positive impact on the availability and rational use of medicines. History of the Essential Medicines List The first country in the world to compose

its EML was Tanzania in 1970. Then in 1975, the World Health Assembly requested WHO to assist member states in selecting and procuring essential medicines, assuring good quality at reasonable cost. Subsequently, the first WHO model list of essential medicines was published in the year 1977 which contained 186 medicines. It stated that essential medicines were "of utmost importance, basic, indispensable and necessary for the health and needs of the population" and criteria for selection were based on efficacy, safety, quality and total cost. The emphasis was laid on disease burden and treatment guidelines as basis for selecting medicines to the EML.

In 1985, the list of essential medicines of the WHO was recognised as important mainly for the public sector and its scope was to guide the procurement, distribution, rational use and quality assurance of medicines. The scope and ambit of WHO EML were gradually widened and the number of medicines in the WHO EML increased over the years. A similar trend is seen with the National List of Essential Medicines (NLEM) of India.

Need for Country Specific EML The WHO EML is a model list.

The decision about which medicines are essential remains a national responsibility based on the country's disease burden, priority health concerns, affordability concerns etc.

Country Specific Disease Burden

The concept of Essential medicines revolves around addressing "priority health care needs" specific to a country. It is therefore important to take into consideration the 'burden' of diseases in that population. The burden of a disease may vary from country to country, so do the priority health care needs. For example, tuberculosis, malaria and diarrhoeal diseases are priority health care concerns in low- and middleincome countries, but it may not be so for high-income countries. On the same lines, trypanosomiasis may be a priority health care concern in the African region where it is endemic but not so in India.

Priority Health Care Concerns: Variation within a Country

In a country like India, which has a large geographic area with huge diversity in climate, food habits, culture etc, there may be differences in health care priorities within the country, across different regions. For example, kala-azar is more prevalent in Bihar whereas Japanese encephalitis is more prevalent in Assam. Therefore, medicines for priority health care conditions for different regions of the country should be considered for inclusion in NLEM.

Affordability Concerns Affordability of a medicine in a population depends on a number of factors such as the status of the health care infrastructure and socioeconomic status of the people and health insurance.

There may be situations where some medicines or formulations may have advantage over other medicines/ formulations in similar class, but the high cost differential and unaffordability by common man may not merit their inclusion in NLEM.

An example is given below: The injectable iron preparations used for iron deficiency are Iron dextran, iron sucrose, and ferric carboxymaltose. Iron dextran is the cheapest of the three but has substantial safety concerns due to risk for anaphylaxis. Iron sucrose is a bit costlier but is much safer. Ferric carboxymaltose has the least safety concern and can deliver the maximum amount of iron. Ferric carboxymaltose is however, very expensive and hence it does not justify inclusion. Considering comparative cost-effectiveness, out of the three, iron sucrose has been included in NLEM 2015.

There may be a situation where one formulation of a medicine may have higher cost but with significant advantage of safety and/or efficacy over the other formulation of the same medicine. Because of the advantage, the costlier formulation may be included in the list. However, considering the socioeconomic conditions, the less expensive, other formulation may also find a place in the list. An example is given below: Injectable amphotericin B is available

in conventional as well as lipid/ liposomal forms. Lipid/ liposomal formulation has advantage over the conventional form because of its relatively less renal toxicity. However considering the advantage, as well as socioeconomic conditions, both lipid/ liposomal and conventional forms have been included.

Purpose of the National List of Essential Medicines

The NLEM may have multiple uses. It can:

1. Guide safe and effective treatment of priority disease conditions of a population

2. Promote the rational use of medicines

3. Optimize the available health resources of a country It can also be a guiding document for:

a) State governments to prepare their list of essential medicines

b) Procurement and supply of medicines in the public sector

c) Reimbursement of cost of medicines by organizations to its employees

d) Reimbursement by insurance companies

e) Identifying the 'MUST KNOW' domain for the teaching and training of health care professionals

Ensuring Affordability and Availability of Medicines listed in NLEM

Listing of a medicine in NLEM necessitates its affordability and availability at all times, in adequate amounts, with assured quality to meet the health care needs. This is particularly important in India where out of pocket expenditure for healthcare is quite high with inadequate health insurance. NLEM may act as an important tool in government's initiative to make the medicines affordable and available to the public.

Fixed Dose Combinations (FDCs)

As a principle, single medicines are to be preferred. FDCs are included only if the combination is rational and has a proven advantage with respect to therapeutic effect, safety and compliance or in decreasing the emergence of drug resistance. Some examples are, diseases such as malaria, Human Immunodeficiency Virus (HIV) infection/ acquired immunodeficiency syndrome (AIDS), where the emergence of antimicrobial resistance is an important issue, which may be partly caused by poor compliance. In these therapeutic categories, certain FDCs have been considered as essential.

In certain other cases where FDCs are critical for their optimal efficacy, such FDCs are also considered as essential. For example, FDC of levodopa and carbidopa, and FDC of amoxicillin and clavulanic acid.

Revision of NLEM– Detailed Procedure

In order to revise the NLEM 2011, a Core Committee was constituted by the Ministry of Health and Family Welfare, Government of India, vide order no: 12-01/13-DC (Pt.98) Dated May 7, 2014 under Chairmanship of Dr VM Katoch, the then Secretary, Department of Health Research and Director General, Indian Council of Medical Research. Dr YK Gupta, Professor and Head, Department of Pharmacology, AIIMS, New Delhi was the Vice-chairman. The Core-Committee in its first two meetings, discussed in detail the modalities to be followed for revision of NLEM and prepared guiding principles and criteria for the revision of NLEM 2011 as under.

Criteria for Inclusion of a Medicine into NLEM 2015

For inclusion of a medicine into NLEM, the medicine should:

1. Be licensed/ approved in the country by Drugs Controller General (India)

2. Be useful in disease which is a public health problem in India

3. Have proven efficacy and safety profile based on valid scientific evidence

4. Be comparatively cost effective

5. Be aligned with the current treatment guidelines for the disease

6. Be stable under the storage conditions in India Medicines recommended under National Health Programmes of India are considered for inclusion in NLEM.

In addition, the following criteria were also considered:

1. When more than one medicine are available from the same therapeutic class, preferably one prototype/ medically best suited medicine of that class to be included after due deliberation and careful evaluation of their relative safety, efficacy, costeffectiveness.

2. Price of total treatment to be considered and not the unit price of a medicine

3. FDC are not included unless the combination has unequivocally proven advantage over single compounds administered separately, in terms of increasing efficacy, reducing adverse effects and/or improving compliance

4. The medicine in NLEM will be based at P/S/T level of health care according to treatment facilities and training, experience and availability of health care personnel at these levels

Criteria for Deletion of a Medicine

A medicine will be deleted from NLEM 2011 in the following conditions

1. The medicine has been banned in India.

2. If there are reports of concerns on the safety profile of a medicine

3. If medicine with better efficacy or favourable safety profile and better cost-effectiveness is now available

4. The disease burden for which a medicine is indicated is no longer a national health concern

5. In case of antimicrobials, if the resistance pattern has rendered a medicine ineffective.

2.LITERATURE REVIEW

- ***Mathew et al (2021)*** conduct a prospective observational study of the prescribing trends of fixed dose combinations, to assess their rationality and inclusion in essential medicines list and national list of essential medicines. Out of 1000 case sheets studied a total of 435 fixed dose combinations were prescribed, all by their brand names during hospitalization. Fixed dose combinations given for infectious diseases were 29.57 % and for respiratory disorders 20.82 %. Those included in WHO essential medicines list 2017 were 11.72 %, while 10.57 % were in the national list of essential medicines 2015 and 17.7% were approved by the US FDA, 56.78 % by DCGI. Rational fixed dose combinations were 38.62 % and 61.37 % were irrational. In the discharge medication chart, miscellaneous agents (19.72 %) and drugs for infectious disorders (15.80 %) were the commonly prescribed fixed dose combinations. Among these 8.25 % were listed in WHO essential medicines list 2017, 6.78 % in the national list of essential medicines 2015 and 15.04 % fixed dose combinations were approved by the US FDA, 53.98 % by the DCGI. Rational combinations were 36.87 % and 63.12% were irrational. Rationality in combining drugs as fixed dose combinations and their appropriate use can reduce pill burden, cost and improve patient adherence.

- ***Chandel et al. 2020***, conduct a prospective observational study to know the awareness of physicians in prescribing rational FDCs was the need of the hour in order to assess the prescribing trends and rationality of FDCs. A total of 2496 drugs were prescribed in 1008 prescriptions, of which 945 (37.82%) were FDCs with an average of 0.93 ± 0.94 (mean ± SD) per prescription. Of 945, 67 (7.09%) were included in National List of Essential Medicine 2015 considered as rational. The number of prescriptions containing one or more FDCs was 629 (62.40%). FDCs were more frequently prescribed to male patient's (54.92%) and in the age group of 18–30 years (33.44%).

FDCs containing a proton pump inhibitor were prescribed most frequently (16.29%) followed by nonsteroidal anti-inflammatory drugs (13.96%) and multivitamins (7.83%). This study concluded that Prescribing irrational FDCs was very common, and hence there is an obvious need to update our prescribers about the irrationality of FDC and motivate them to develop a habit of rational prescribing.

- ***Shrestha R et al 2020***, conduct a cross-sectional study to evaluate the FDCs and its utilization in medicine department of tertiary care hospital. Oral FDCs were used in 27.08% of admitted patient's . A total of 295 FDCs were prescribed in 208 patient's with 44 FDC items in 58 different brand names. Categorically, the most commonly used FDCs were of analgesics (34.24%) followed by antibiotics (25.76%) and vitamin supplements (22.71%). The 27.27% of FDCs prescribed contain more than two active pharmaceutical ingredients (APIs) up to nine and the highest number of APIs were found in vitamin supplements. All FDCs were prescribed in the brand names. The very few 2.27% and 4.55% of FDCs were prescribed from the essential medicine list of Nepal and world health organization, respectively. This study concluded that the use of FDCs listed in essential medicine list was very poor. Similarly, generic prescribing was also zero. The regulatory body must study the rationality of FDC before production, marketing, importing, and utilization in hospital.

- ***Gupta R et al 2018***, conduct a cross-sectional observational study to assess the rational use of fixed dose drug combinations in hypertension. about sixteen different anti-hypertensive FDCs were observed in the prescriptions of 92 patient's during six-month period. It was observed that about 93.75% of FDCs were dual drug combinations. Among the dual drug combinations, most commonly used combination was Olmesartan (ARB; Angiotensin receptor blocker) + Amlodipinine (Calcium channel blocker) in 17.4% of patient's . It was also observed that among the 16 different anti-hypertensive

fixed dose combinations analysed, 12 FDCs (75%) were found to be rational and 4 FDCs (25%) were found to be irrational. In the present study it was found that 75% of the FDCs prescribed were rational and 25% were irrational. Therefore, before marketing the FDCs proper assessment of their efficacy, safety and rationality should be done.

- ***Krunal Dalal et al 2016***, conduct a a prospective, observational study to assess rationality of FDCs enlisted in CDSCO list and marketing in India according to pharmacokinetic (FD) and pharmacodynamic (FD) reasoning and WHO rationality criteria. Out of total 264 FDCs selected, maximum number of combinations (112) were approved in 2010. Oral dosage form was found to be maximum with 200 (75.75%) combinations. According to schedules, 154 (58.33%) combinations were categorized under schedule H. There were 210 (79.54%) FDCs that had two API which was found to be maximum, whereas, only 3 (1.13%) combinations had 5 API. We could find possible PK and PD interactions in between API of 10 (3.78%) and 73 (27.65%) combinations respectively on basis of standard textbooks and references. Similarly dose reduction in API was seen in 58 (21.96%) FDCs. There were 123 (46.59%) FDCs had chances of increased ADRs due to its API. Out of 264 combinations, 52 combinations were rational (6-9), 75 combinations were semi-rational (3-<6) and 137 combinations were found to be irrational (0<3). This study concluded that that majority of combinations approved in last six years were found to be semi-rational and irrational. It is important to carry out detailed study in this area to establish the fact and increase rationality of combinations

- ***Yadav et al, 2016*** conducted a study to study the prescribing frequency of FDCs and to evaluate the rationality of FDCs prescribed in psychiatric patient's . This prospective study was carried out in Pharmacology and Psychiatry Department of a tertiary care

teaching hospital in Rajasthan, India. The data were collected in a case record form from patient's of all ages and from either sex, who visited the outpatient department of psychiatry. Data were analyzed with the help of well known comprehensive seven-point criteria by Panda et al, which were developed by carefully studying the guidelines of the World Health Organization and Committee for Proprietary Medicinal Products, Europe. Total 383 drug formulations were prescribed in 200 patient's of which 107 (27.93%) were in the form of FDCs. Most frequently prescribed FDC was escitalopram + clonazepam (22.44%), followed by amitriptyline + chlordiazepoxide (13.08%). The maximum score for the seven-point criteria for assessing the rationality of FDCs was 14, with each criterion carrying a score of 2. Scores obtained in this study ranged between 5 and 14 with an average of 8.79. Most of the FDCs were irrational according to the criteria used and only 28.57% of the FDCs were found to be rational considering safety and efficacy as the most important criteria for rationality. So, drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs.

- ***Angelika Batta et al 2018***, conducted a study was carried out in the outpatient department of medicine at Mahatma Gandhi Medical College and Hospital, Jaipur. Total 500 prescriptions were collected for the duration of 6 months, starting from February 2014 and assessed. The data was analyzed using Microsoft Office Excel® version 2007. Results: The data analysis reflected that 60% of prescriptions analyzed contained FDCs; revealing that significantly high number of patient's received FDCs. The total number of FDCs in a prescription was also greater (mean = 1.82). Out of 60 FDCs prescribed only three of them were enlisted in the Essential Medicine List of World Health Organization and Government of India. Conclusion: The increased trend in using irrational FDC warrants a drug regulatory body in every hospital to ameliorate

the free flow of irrational FDCs. Awareness programs focusing on deleterious consequences related to irrational use of medicines should be made.

- ***Goswami, et al 2013***, conducted a study was carried out among resident doctors working at Civil Hospital, Ahmedabad, a tertiary care teaching hospital. One hundred resident doctors from the departments of medicine, obstetrics and gynaecology, surgery, paediatrics, skin and psychiatry, who gave their informed consent, were enrolled. A prevalidated questionnaire regarding knowledge, attitude and prescribing practice of fixed dose combinations was filled up. Data was analyzed with suitable statistical tests. Out of the 100 residents recruited for the study, 34, 33 and 33 residents were selected from the 1st, 2nd and 3rd year respectively. The resident doctors were not aware about all of the advantages and disadvantages of FDCs. On an average, only 31% of the residents(lowest 16% among 1st year residents) had knowledge about the Essential Medicine List (EML). Knowledge about rationality of given FDCs was lacking in 81% of the residents. Only 47% could name a single banned FDC in India. Common sources of information about FDCs were medical representatives, colleagues/peers, the Monthly Index of Medical Specialities (MIMS) and Continuous Medical Education (CMEs). Amajority of residents(96%) agreed that FDCs should be allowed to be marketed. The residents opined that most commonly prescribed FDCs were of antimicrobial drugs, amongst which amoxicillin + clavulanic acid was the most frequent. There is need to improve knowledge about rationality, EML, usage and banned FDCs in post graduate medical students to promote the rational use of drugs.

- ***Ishrar et al 2015***, conducted assessing the rational usage of fixed dose combinations in community pharmacies by collection and evaluation of FDCs by using seven-point assessment scale, and development of FDC education tool for practicing rational use. The six months prospective interventional study, carried at community pharmacies

where different FDCs were collected. All data regarding demographics details were collected in a suitably planned data collection form, base line survey, first visit and second visit was conducted using ten point questionnaires. Based on responses awareness was provided for appropriate use through FDCs educational tool. The data obtained were entered in Microsoft excel and graph pad instat software, the score of base line was compared with second follow up using Wilcoxon matched pair test. Out of 404 FDCs collected 144 meets the criteria of rationality. Significant improvement ($p < 0.0001$) in the knowledge, attitude, and practice in the study group showed that pharmacist education at community pharmacies. Similarly a significant improvement ($p < 0.05$) was observed, also assessed the rationality among community pharmacies. In conclusion development of fixed-dose combinations is becoming increasingly important from public health perspective. It is prerequisite in order to educate every working pharmacist about the rationality of FDCs and safeguard patient health outcomes.

3.AIM AND OBJECTIVES

Aim

- To analyze the current prescribing trends and rationality of fixed dose combinations.

Objectives

- FDA classification of FDCs Distribution
- Number of FDCs per prescription.
- Frequently prescribed FDCs
- FDCs included in NLEM 2015 and WHO EML 2021.
- Rationality Scoring scale of Fixed Dose Combinations.

4.PLAN OF WORK

The present dissertation work was planned in 4 phases and to be carried out for a period from November 2021 to February 2022. The proposal was designs as given below.

PHASE I

- Initial study to identify the scope of work.
- Literature Survey.
- Preparation of study protocol.

PHASE II

- Approval of selected title in consultation with hospital and institutional guide.
- Approval from the hospital authorities and human ethics committee.
- Design the data collection and perform pilot testing with the design form.

PHASE III

- Obtain the patient data relevant to study from patient medical records, treatment chart or case sheet, patient interview or patient follow up.
- Data collection.

PHASE IV

- Compilation and correlation of baseline data.
- Analyses the data using appropriate statistical tools.
- Report the data analyzed.

5.METHODOLOGY

This chapter is comprised of the study design, site, sample of the study population data collection, data analysis etc.

Study design and site:

A Prospective, Observational Study design was conducted in general medicine department of the National hospital, Calicut. The study design consists of questionnaires.

- Demographic data and relevant medical history were obtained from all patient's case sheet and medical records.

Study period:

The current Prospective, Observational Study was carried out at National hospital, Calicut over a period from November 2021 to February 2022.

Study Population:

The study involved 325 out-patient's prescription in general medicine department of National Hospital.

Study criteria:

Inclusion criteria

- All the prescriptions the all-age group and both gender containing oral FDCs were separated and required data were copied in data collection form at the time of out-patient hospital visit.

Exclusion Criteria

- Categories of FDCs like parenteral fluids used for hemodialysis & peritoneal dialysis, veterinary and cosmetics from Dermatology.

Source of data:

All the necessary and relevant information were collected from out-patient prescription and patient medical records using the data collection form.

Study Prescription analysis Tools:

- The EML list of WHO (World Health Organisation) 2021 and NLEM (National List of Essential Medicines) 2015 were used for study.
- Assessment of FDCs by WHO Rationality Scoring Scale. The rationality of the FDCs were assessed using a 7-point scale developed based on WHO guidelines which were, inclusion in WHO EML; NLEM; (both/none), Dose appropriateness of the FDC (appropriate/inappropriate). Safety and efficacy of the FDC (safe/efficacious), Pharmacokinetics of FDCs (altered/unaltered), Mechanism of action, (similar/ complementary).

Sr.no	Rationality Criteria	Yes	No
1	API from NLEM and WHO EML	All API (+1) At least one API (0.5)	0
2	Dose of API appropriate for intended use	+1	0
3	Proportion of API appropriate for intended use	+1	0
4	API should have different mechanism of action	+1	0
5	PK and PD interaction	Favorable(+1) Not favorable(-1)	0
6	FDC facilitate dose reduction of API	+1	0
7	FDC facilitate adverse drug reaction	+1	0

[Table/Fig-1]: Assessment of FDCs by Rationality Scoring Scale.
Maximum score= 9, Minimum score= 0
FDCs were graded as Irrational (0-<3), Semi-rational (3-<6), Rational (6-9).

Study procedure:

All the patient's /patient's attender gave informed written consent prior to their inclusion in this study. The study involved 325 patient's prescription in general medicine department. Data were collected in between duration and hospital name.

Ethical Approval

The ethical clearance was approved from institutional ethical committee and hospital authority has sanctioned.

Statistical analysis

The collected data was analyzed by using Microsoft Excel 2010, and results were expressed in number and percentage by using table and bar-diagram.

6.RESULTS

General description

The present study was carried out in out-patient general medicine of National hospital, Calicut. We were recruited 325 patient's prescription according to the inclusion criteria.

SOCIO DEMOGRAPHIC CHARACTERISTIC DISTRIBUTION

Age wise data distribution data for FDCs

The age wise distribution was done in a total of 325 patient's were taken in this study. In > 18 years, age group were 28 (8.62%), In 19-30 years, age group were 32 (9.58%), In 31-45 years age group were 80 (24.62%), In 46-60 years age group were 98 (30.15%) and above 60 years age group were 87 (26.77%). The majority of general medicine department patient's were in age group of 46-60 years old patient's . The mean age was 43.03±18.40 years.

Table 1: Age wise data distribution data for FDCs

S.NO	AGE CATEGORY	TOTAL	%
1	> 18 years	28	8.62
2	18-30 years	32	9.85
3	31-45 years	80	24.62
4	46-60 years	98	30.15
5	60 years Above	87	26.77
	Total	325	100
Mean±SD		**43.03±18.40**	

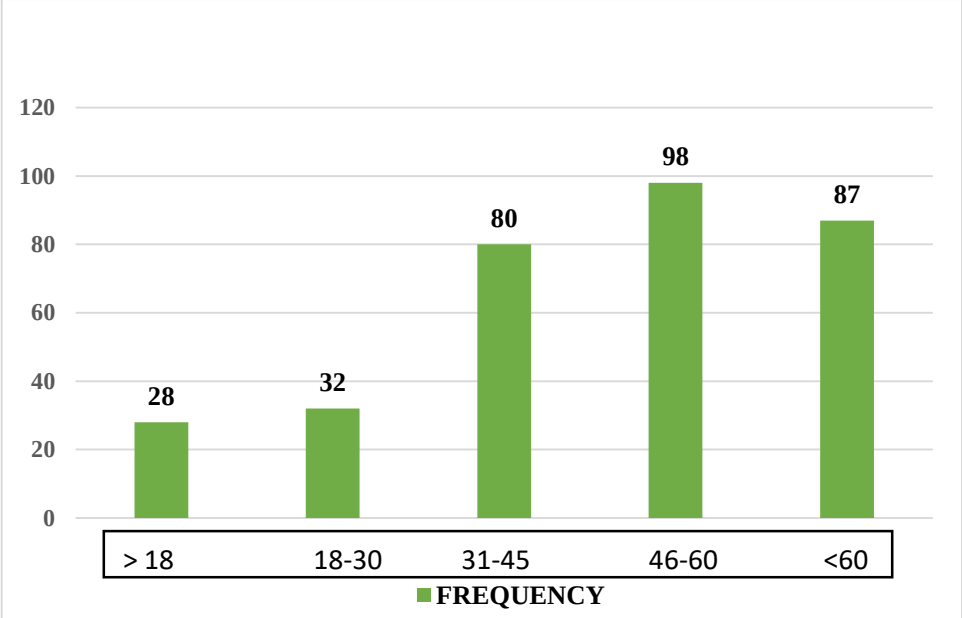


FIG 1 : AGE GROUP OF FDCs

Gender wise data distribution data for FDCs

The study reveals about gender wise distribution of 325 patient's . In that the male patient's were 176 (54.15%) and female patient's were 149 (45.85%). In general medicine, male patient's were more in number.

Table 2: Gender wise data distribution data for FDCs

S.NO	GENDER	NO OF PATIENT'S	%
1	Male	176	54.15
2	Female	149	45.85
	Total	325	100

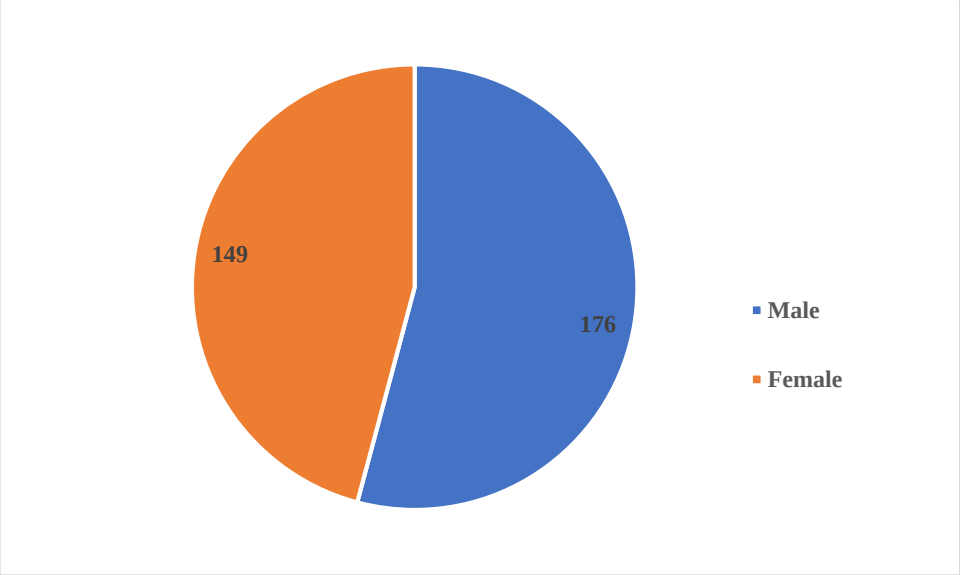


FIG 2: GENDER WISE DATA DISTRIBUTION DATA FOR FDCs

Occurrence of no of FDCs per prescription

A total of 325 patient's prescription, 468 FDCs were found. In those 214 (65.85%) patient's prescription contains 214 (45.73%) of one FDC. Followed by, 82 (25.23%) of patient prescription contains 164 (35.04%) of two FDCs, 26 (8%) of patient's prescription contains 78 (16.67%) of three FDCs, 3 (0.92%) of patient's prescription contains 12 (2.56%) of four FDCs. These results showed that most of the patient's prescription had 1 FDC.

TABLE 3: OCCURRENCE OF NO OF FDCs PER PRESCRIPTION

S.NO	NO OF FDCs	NO OF PATIENT'S	%	FREQUENCY	%
1	1	214	65.85	214	45.73
2	2	82	25.23	164	35.04
3	3	26	8.00	78	16.67
4	4	3	0.92	12	2.56
	TOTAL	325	100	468	100

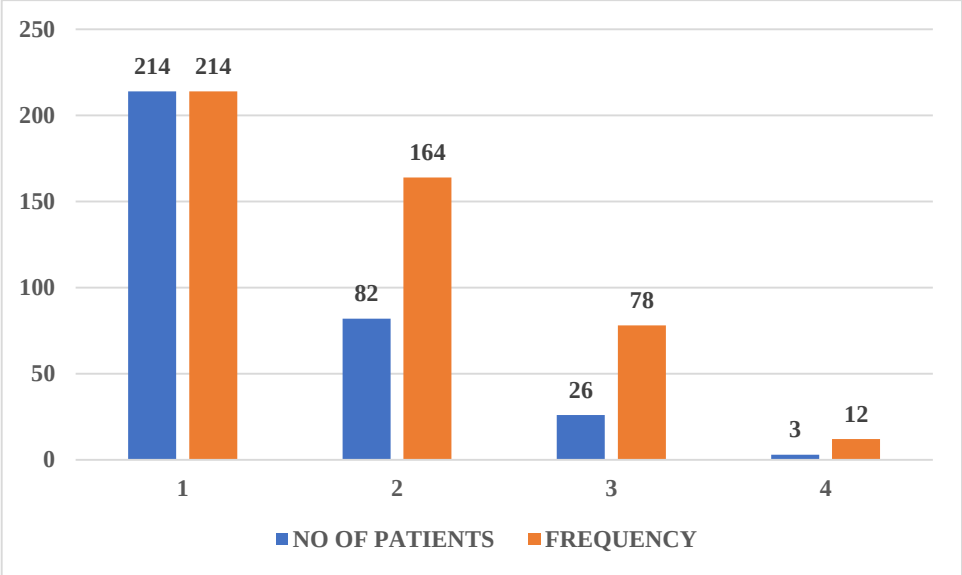


FIG 3: OCCUERANCE OF NO OF FDCs PER PRESCRIPTION

No of APIs per prescription FDC

Table 4 states no of Active Pharmaceutical ingredients per prescription. Out of 468 FDCs, 325 (69.44%) of FDCs had two APIs, followed by 104 (22.22%) of FDCs had 3 APIs and 39 (8.33%) of FDCs had 4 APIs. These results showed, most of the FDCs had 2 APIs.

TABLE 4: NO OF APIs PER PRESCRIPTION

S.NO	NO OF APIs PER FDC	FREQUENCY	%
1	Two	325	69.44
2	Three	104	22.22
3	Four	39	8.33
	Total	**468**	**100**

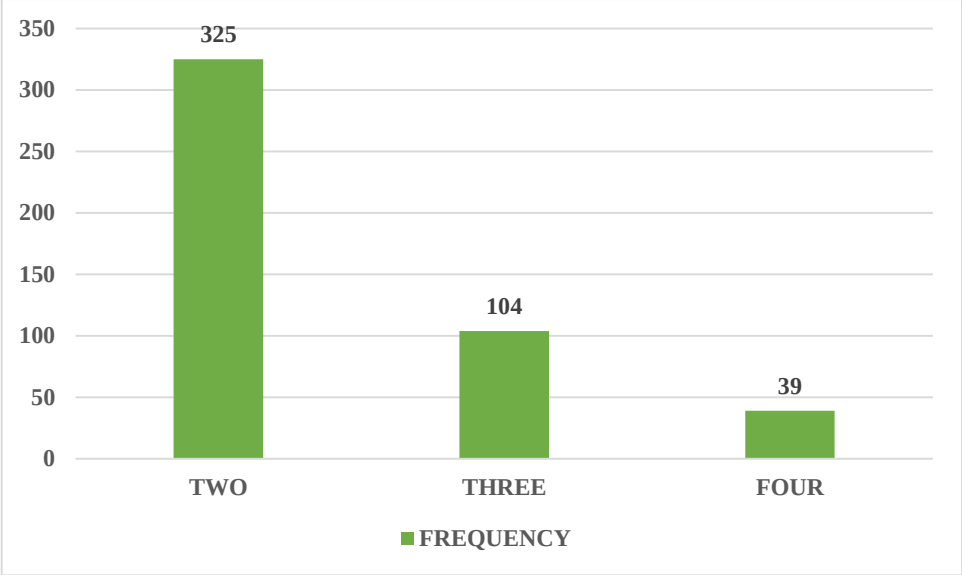


FIG 4 : NO OF APIs PER PRESCRIPTION

\Dosage form of FDCs

Out of 468 patient's prescription, most of the patient's prescription 357 (76.28%) had oral dosage form of FDCs, followed by 86 (18.38%) of patient's prescription had topical dosage form of FDCs and 25 (5.34%) of patient's prescription had parenteral dosage form of FDCs.

TABLE 5: DOSAGE FORM OF FDCs

S.NO	DOSAGE FORM OF FDCs	FREQUENCY	%
1	Oral	357	76.28
2	Parenteral	25	5.34
3	Topical	86	18.38
	TOTAL	**468**	**100**

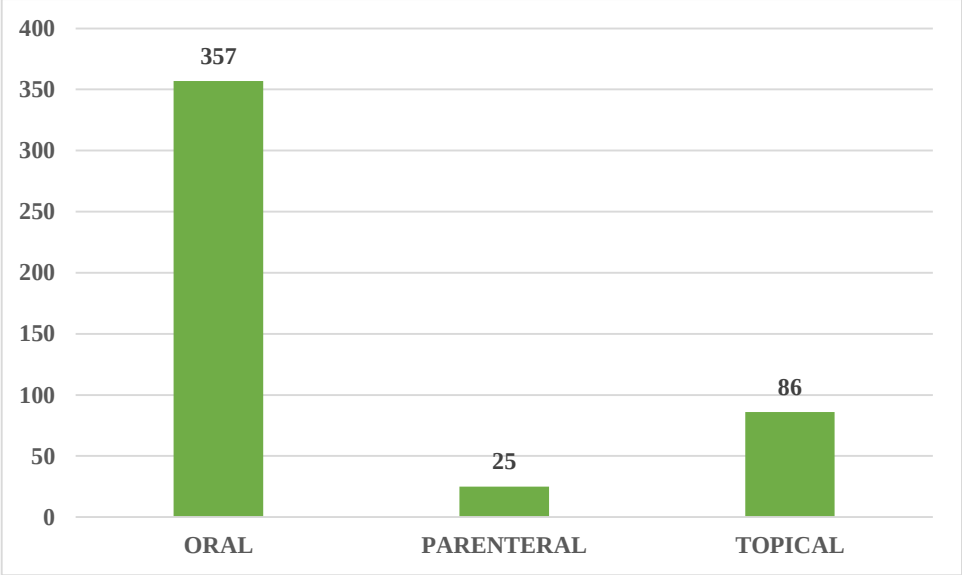


FIG 5: DOSAGE FORM OF FDCs

Classification of FDC

This study reveals that FDA classification of FDCs in patient's prescription. Out of 468 FDCs, most of the FDCs 116 (24.79%) were in analgesics, followed by 104 (22.22%) of FDCs in vitamin supplements, 74 (15.81%) of FDCs were in antibiotics, 67 (14.32%) of FDCs were in cough preparations, 35 (7.48%) of FDCs were in antacids, 21 (4.49%) of FDCs were in anti-hypertensives, 19 (4.06%) of FDCs were in anti-diabetics, 14 (2.99%) of FDCs were in anti-parkinsonism and 8 (1.71%) of FDCs were in anti-tubercular drugs.

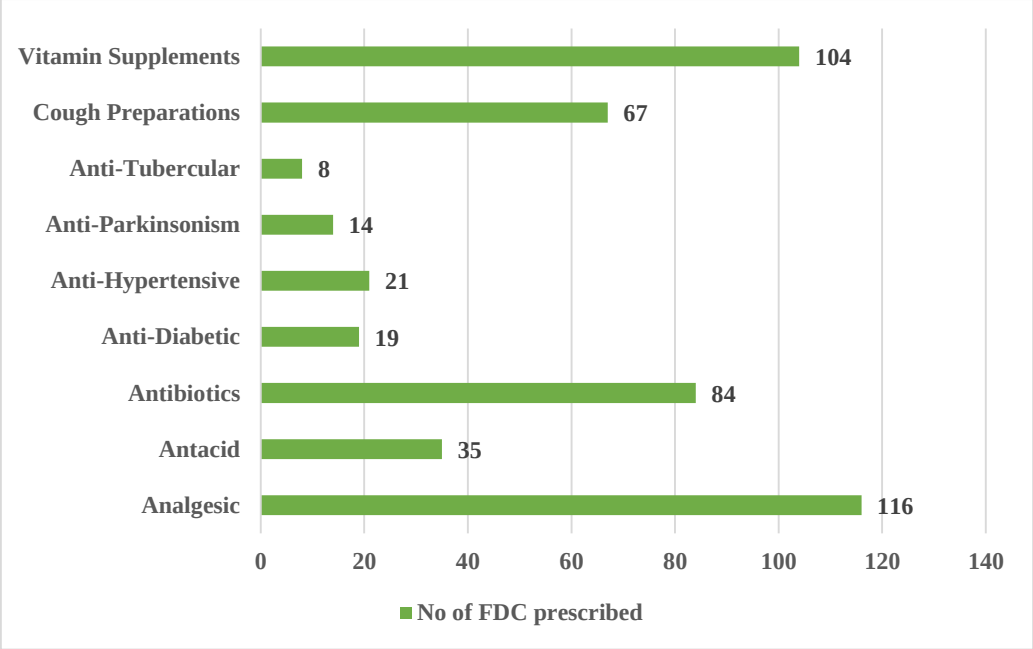


FIG 6: NO OF FDC PRESCRIBED

TABLE 6: NO OF FDC PRESCRIBED

S.no	FDC category	No of FDC prescribed	%	No of FDC prescribed in generic name	%	No of FDC prescribed in brand name	%
1	Analgesic	116	24.79	8	1.71	108	23.08
2	Antacid	35	7.48	9	1.92	26	5.56
3	Antibiotics	84	17.95	8	1.71	76	16.24
4	Anti-Diabetic	19	4.06	6	1.28	13	2.78
5	Anti-Hypertensive	21	4.49	4	0.85	17	3.63
6	Anti-Parkinsonism	14	2.99	3	0.64	11	2.35
7	Anti-Tubercular	8	1.71	8	1.71	0	0.00
8	Cough Preparations	67	14.32	0	0.00	67	14.32
9	Vitamin Supplements	104	22.22	0	0.00	104	22.22
	Total	**468**	100	**46**	9.83	**422**	90.17

Prescription with Generic name Vs Brand Name

Out of 468 FDCs, most of the FDCs were prescribed in 422 (90.17%) brand name and 46 (9.83%) of FDCs were prescribed in generic name. The detailed generic and brand name of FDCs in prescription were in below.

In analgesic category, 8 (1.71%) of FDCs prescribed in generic name and 108 (23.08%) of FDCs prescribed in brand name, in antacids 9 (1.92%) of FDCs prescribed in generic name and 26 (5.56%) of FDCs prescribed in brand name, in antibiotics 8 (1.71%) of FDCs prescribed in generic name and 76 (16.24%) of FDCs prescribed in brand name, in anti-diabetics 6 (1.28%) of FDCs prescribed in generic name and 13 (2.78%) of FDCs prescribed in brand name, in anti-hypertensives 4 (0.85%) of FDCs prescribed in generic name and 17 (3.63%) of FDCs prescribed in brand name, in anti-parkinsonism category, 3 (0.64%) of FDCs prescribed in generic name and 11 (2.35%) of FDCs prescribed in brand name, in anti-tubercular drugs 8 (1.71%) of FDCs prescribed in generic name and no FDCs prescribed in brand name, in cough preparations 67 (14.32) and vitamin supplements 104 (22.22%) all FDCs were prescribed in brand name only.

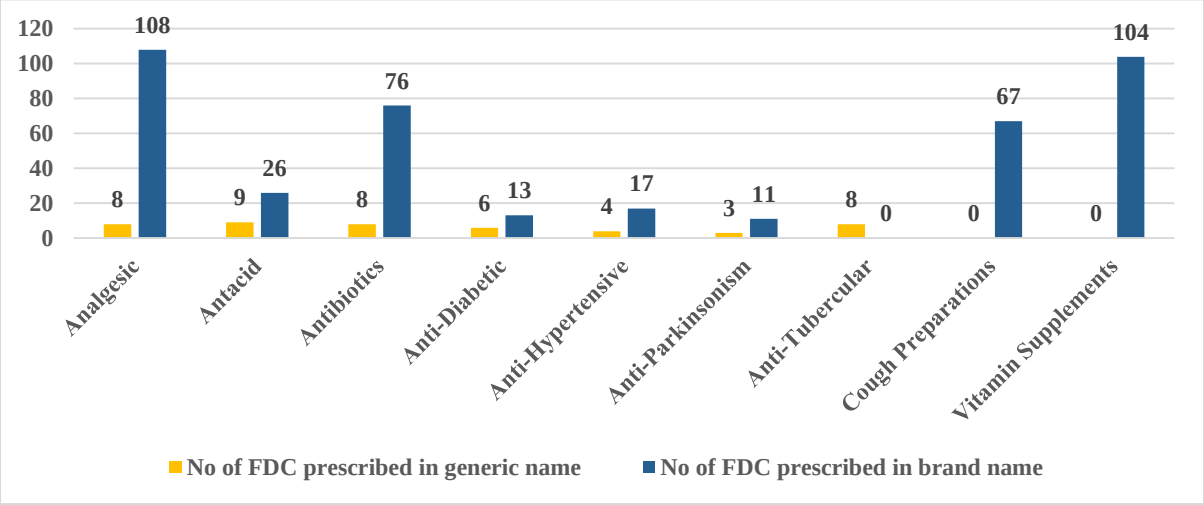


FIG 7: FDCs PRESCRIBED BY GENERIC NAME Vs BRANDS NAME

Commonly Prescribed FDCs

Table 8 reveals most commonly prescribed FDCs. In that, most of the FDCs 41 (8.76%) were Tab.Ibuprofen 400mg + Paracetamol 325mg, followed by 37 (7.91%) FDCs were Tab.Pantoprazole 40mg + Domperidone 10mg, 35 (7.48%) of FDCs were Tab.Amoxicillin 500mg + Clavulanic Acid 125mg, 29 (6.20%) of FDCs were Tab.Vitb1 5mg +Vit B2 5mg + Vit B3 45mg + Vit B6 1.5mg + Vit B9 1mg + Vit B12 5mcg + Vit A 5000IU + Vit C 75 Mg + Vitamin E 15 IU, 28 (5.98%) of FDCs were Tab.Cefpodoxime 200mg + Clavulanic Acid 125mg, 23 (4.91%) of FDCs were Tab.Aceclofenac 100mg+Paracetamol 500mg, 21 (4.49%) of FDCs were Tab.Cefixme 2000mg + Clavulanic Acid 125mg.

TABLE 8: COMMONLY PRESCRIBED FDCs

S.NO	COMMONLY PRESCRIBED FDC	FREQUENCY	%
1	Tab.Cefpodoxime 200mg + Clavulanic Acid 125mg	28	5.98
2	Tab.Amoxicillin 500mg + Clavulanic Acid 125mg	35	7.48
3	Tab.Cefixme 200mg + Clavulanic Acid 125mg	21	4.49
4	Tab.Calicum Citrate 1000mg+Magnesium 100mg+Zinc 4mg+Vitamin D3IU	27	5.77
5	Tab.Vitb1 5mg +Vit B2 5mg + Vit B3 45mg + Vit B6 1.5mg + Vit B9 1mg + Vit B12 5mcg + Vit A 5000IU + Vit C 75 Mg + Vitamin E 15 IU	29	6.20
6	Ibuprofen 400mg + Paracetamol 325mg	41	8.76
7	Tab.Aceclofenac 100mg+Paracetamol 500mg	23	4.91
8	Tab.Pantoprazole 40mg + Domperidone 10mg	37	7.91
	TOTAL	**241**	51.50

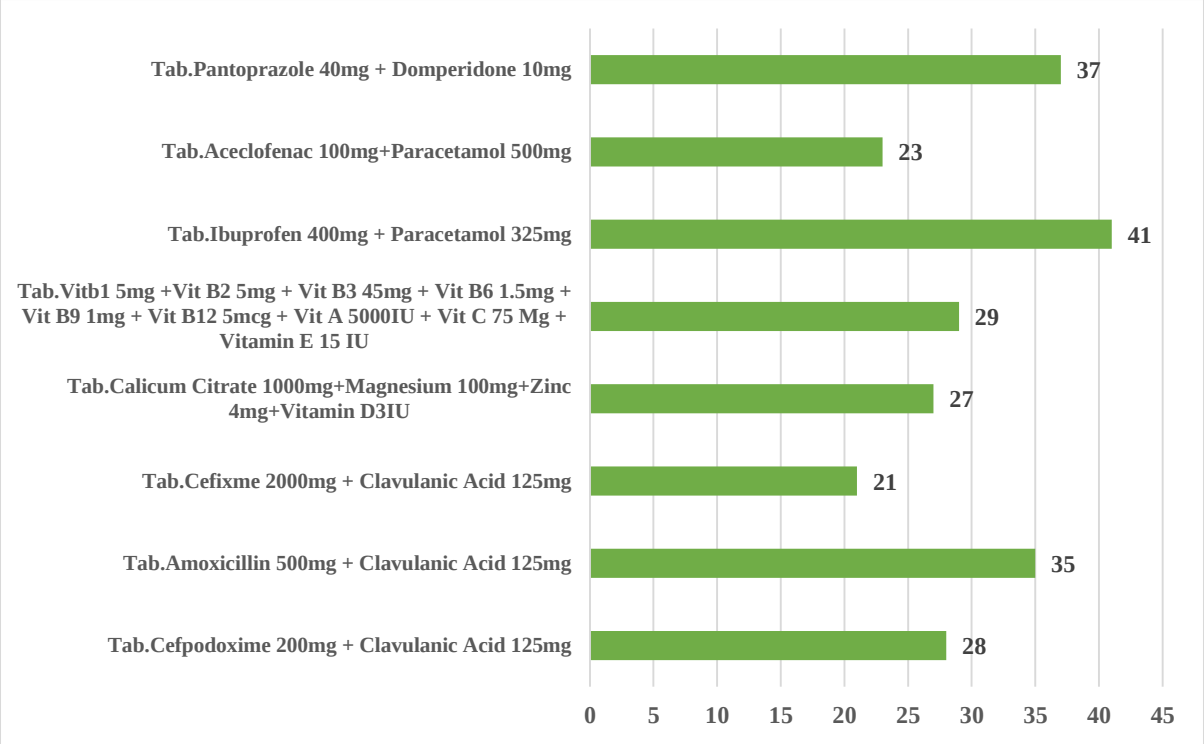


FIG 8: COMMONLY PRESCRIBED FDCs

Rationality Criteria

Table 9 reveals the rationality criteria of 468 FDCs. In rationality criteria, 184 (39.32%) of FDCs in EML from WHO and 153 (32.69%) of FDCs were from NLEM. 245 (52.35%) of FDCs were in appropriate intended dose, 145 (30.98%) of FDCs were in appropriate indented use, 84 (17.45%) of FDCs have different mechanism of action, 67 (14.32%) of FDCs have pharmacokinetic and pharmacodynamic interactions, 119 (25.43%) of FDCs facilitates the dose reduction of API and 135 (28.85%) of FDCs facilitates adverse drug reactions.

TABLE 9: RATIONALITY CRITERIA

S.NO	RATIONALITY CRITERIA	FREQUENCY	%
1	API from EML of WHO	184	39.32
2	FDCs in EML of NLEM	153	32.69
3	Dose of API appropriate for intended use	245	52.35
4	Proportion of API appropriate for intended use	145	30.98
5	API should have different MOA	84	17.95
6	PK and PD interaction	67	14.32
7	FDC facilitate dose reduction of API	119	25.43
8	FDC Facilitate Adverse Drug Reaction	135	28.85

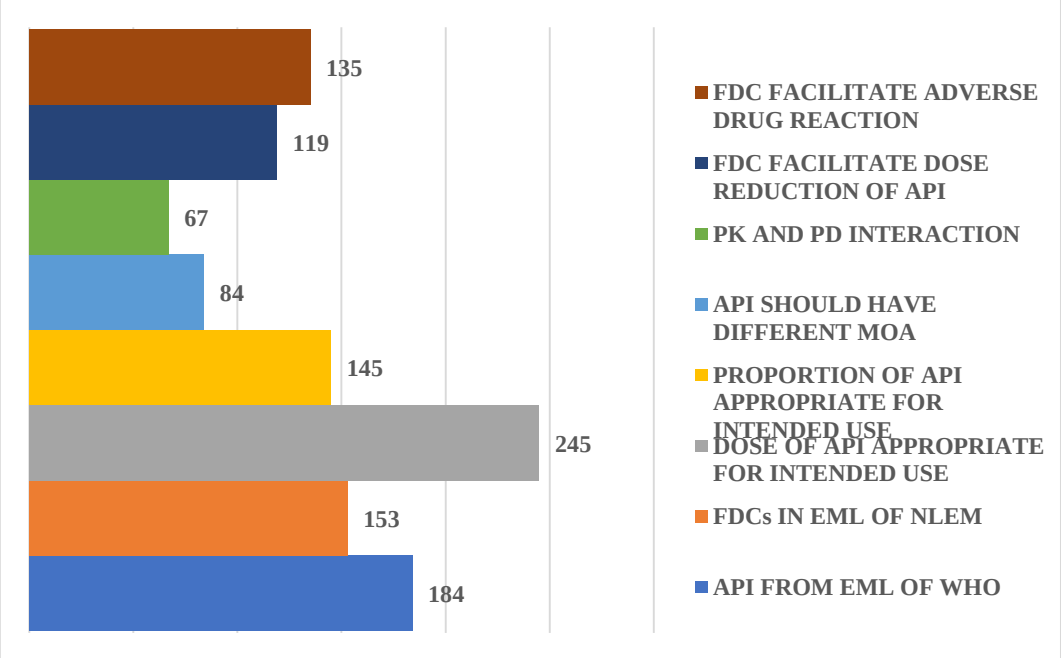


FIG 9: RATIONALITY CRITERIA

Rationality

Table 10 showed rationality of FDCS. The most of FDCs were irrational 196 (41.88%). Out of 468 FDCs 105 (22.44%) of FDCs were rational and167 (35.68%) of FDCs were semi-rational.

TABLE 10: RATIONALITY

S.NO	RATIONALITY CRITERIA	FREQUENCY	%
1	Rational	105	22.44
2	Semi-Rational	167	35.68
3	Irrational	196	41.88
	Total	468	100

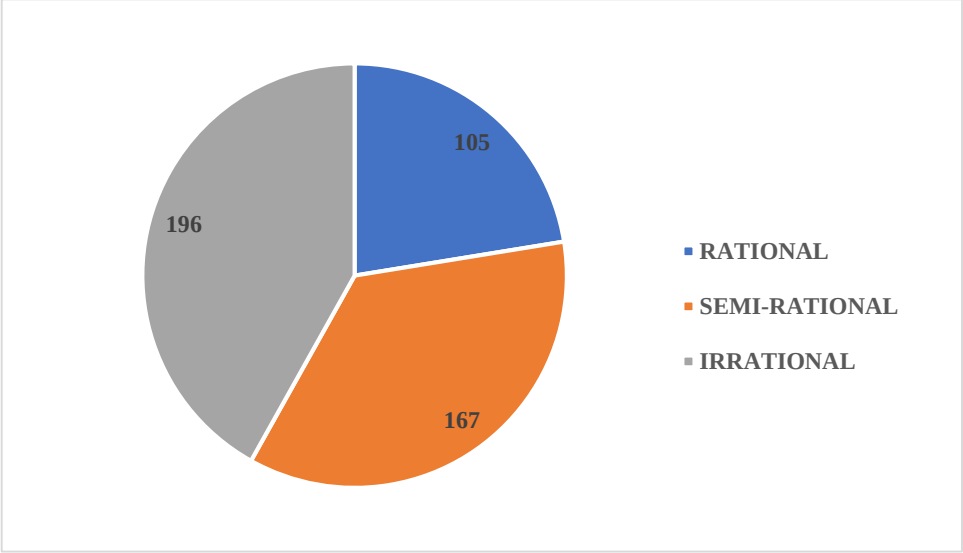


FIG 10: RATIONALITY

7. DISCUSSION

Present study was done on assessment of FDCs with special inference to their rationality. Most of the studies on fixed dose combinations were related to prescribing pattern of combinations in different set up and diseases. In our study FDCs were comparatively found to use in higher in males 54.15%. In age group of 46-60 years old. y. Similarly, a study of Ahmedabad, India showed high number of FDCs prescribed to 31 to 49-year patients (23.7%). (Balat J D et al., 2014)The reason could be the higher availability of adult dose FDCs or the higher number of an adult aged patient admitted to the medicine department.

Out of total 468 FDCs taken for rationality, 357 (76.28%) maximum combinations were in oral dosage form followed by 86 (18.38%) in topical and rest 25 (5.34%) in parenteral dosage form. Similar result was seen in Balat et al., combinations were most commonly prescribed by oral route (92.7%) followed by topical (5.9%) and parenteral (1.4%) routes ($p < 0.001$). According to Shah et al., all cardiovascular fixed dose combinations have oral dosage form (Shah S et al., 2015).

The 34.15% of patients received more than one FDC up to four, and 25.23% of prescribed FDCs contain more than two APIs up to four in our study. A study carried out in India reported increased in adverse reaction in more than half of FDCs, while the FDCs in that study and of our is not compared. Therefore, the appropriate need-based selection and use of FDC is required. However, a study among dental clinicians and residents reported that they had poor knowledge and awareness of FDC. (Poudel A et al., 2017). The pharmaceutical company encourages physicians to prescribe their FDC even though they are not required by patients. Therefore, the prescriber should be equipped with appropriate knowledge and skill to rationally prescribe FDCs, and the hospital pharmacist is a desired professional to provide appropriate information regarding medicines in hospital.

Most of the FDCs were prescribed in 422 (90.17%) brand name and 46 (9.83%) of FDCs were prescribed in generic name. FDC prescribing in brand name seems to be easier than in generic. Generic writing requires mentioning doses of composition but the brand name writing directly indicates composition as the specific brand name has specific doses of composition. However, the absence of true knowledge about the composition and dose of API of FDCs leads to harmful consequences. The brand prescribing makes it difficult to arrange and dispense a particular brand by the hospital pharmacy. The generic prescribing and dispensing is desirable in developing countries as it reduces the expense of patients.

In our study 74 (15.81%) of FDCs were in antibiotics , the highest numbers of different brands were found in antibiotic drugs and specifically in the case of amoxicillin 500 mg and clavulanic acid 125 mg tab. The EML of Nepal and WHO both considered this FDC as essential. This combination is considered rational by other studies also. (Pradhal S et al., 2017). Generally, higher use of medicine has higher brand and market competition. On the other hand, the most used antibiotic cefixime 200 mg and clavulanic acid 125 mg tab had two brands; this combination is not listed in both EML of Nepal and WHO. Additionally, this FDC is considered irrational because clavulanic acid is supposed to prevent the destruction of beta-lactam ring of penicillin antibiotics only. The regulatory body is responsible to make criteria and check the rationality of FDCs scrutinously before manufacturing and marketing authorisation.

In our study most of the FDCs 116 (24.79%) were in analgesics, followed by 104 (22.22%) of FDCs in vitamin supplements, 67 (14.32%) of FDCs were in cough preparations, 35 (7.48%) of FDCs were in antacids, 21 (4.49%) of FDCs were in anti-hypertensives, 19 (4.06%) of FDCs were in anti-diabetics, 14 (2.99%) of FDCs were in anti-parkinsonism and 8 (1.71%) of FDCs were in anti-tubercular drugs. among them, vitamin B combination and calcium combination were the majors. Vitamin supplements were commonly used in other studies as well.(Gautam C S et al ., 2008). In case of vitamin supplements, the combination drug was very much similar

to each other, but their combination dosage was different. There were ten brands and equally ten generic items in vitamin supplements. The unique combination compels patients to search for a particular brand. The slight changes in API and dose are probably the marketing strategy of manufacturers to promote their brand. Therefore, patients must be assessed thoroughly about their nutritional deficiency and the requirement of a specific dose of vitamins. The regulatory body must study combinations and doses of FDC before giving approval for marketing. Higher use of nutritional FDCs without proper study can increases financial expenses, unwanted toxicities, and interactions.

The very few 32.69% and 39.32% FDCs were prescribed from EML of NLEM and WHO, respectively, in our study. While it was 12% from EML of WHO and 6.4% from EML of India in the study of South India. There were few FDCs which have a similar composition to EML but their doses were not matched. And, most commonly used five FDCs were also not present in either EMLs. Similarly, the majority of APIs that are 63.41% and 70.75% were not present in EML of Nepal and WHO, respectively. WHO encourages essential medicines use as they are safe, efficacious, cost-effective and able to meet the priority health needs of patients? From the above result, it can be said that either the commonly used FDCs were not safe, efficacious, and cost-effective for priority condition or they were not studied properly and updated EML on a regular basis. The current study emphasised the need to find the rationality and importance of FDCs practiced in the market and update the EML accordingly.

In our study 52.35% of FDCs were in appropriate intended dose, 30.98% of FDCs were in appropriate indented use, 17.45% of FDCs have different mechanism of action. According to WHO, FDCs are rational when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, and adherence or in delaying the development of drug resistance. The combination should act by different mechanism and act as a booster for another. However, 6.81% of FDCs (n=3) that are paracetamol 500 mg and

ibuprofen 400 mg tablet, paracetamol 125 mg and ibuprofen 100 mg per 5 ml, and ampicillin 250 mg and cloxacillin 250 mg capsule have a different mechanism of action and no complementary action. These combinations are considered irrational because the combination does not have synergistic or additive action, rather the side effects are additive (Shah S et al.,2015, Ravichandran A et al., 2017). Additionally, analgesics (24.79%) were the mostly used FDC among all other categories; and Ibuprofen 400 mg and paracetamol 500 mg was the highly used FDC among them. A study conducted in India showed that NSAIDs combination had covered two-thirds of FDCs sold in 2011 to 2012. The combination of two NSAIDs is considered highly undesirable, as it has been found to be associated with gastrointestinal risk. (McGettigan P et al ., 2015) .

In our study the most of FDCs were irrational 196 (41.88%). Out of 468 FDCs 105 (22.44%) of FDCs were rational and167 (35.68%) of FDCs were semi-rational. The study of marketed FDCs rationality is becoming a major concern. The drug and therapeutic committee of the hospital has to be alert and conduct a rigorous study to promote appropriate use of FDC.

8. CONCLUSION

The therapy with FDCs reduce the polypharmacy or pill burden, which in turn can improve patient compliance. However, the rationality and justification of their uses always raises doubt and it can lead to controversial usage of drugs. Most commonly, the clinicians obtain information from the medical representatives apart from obtaining the information through peer group, resources like MIMS, CIMS, and continuing medical education programs. Insufficient or often biased information can lead to inappropriateness in the use of drugs. Strengthening of the regulatory guidelines, provision of continued updated unbiased information about the drug products and their safety should help in minimizing the inappropriate and irrational use of drugs.

Awareness and education about irrational FDCs, FDCs containing banned or controversial ingredients will help develop rational prescribing practices among prescribers. Rational combination of drugs to formulate FDCs and the appropriate use of FDCs can definitely improve adherence to the therapy, safety, and reduce the cost of therapy. However, efforts to increase awareness regarding the correct use of FDCs should be a constant objective for the pharmacists.

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ANNEXURE

CURRENT PRESCRIBING TRENDS AND RATIONALITY OF FIXED DOSE COMBINATIONS IN A SOUTH INDIAN MULTI SPECIALTY HOSPITAL - AN OBSERVATIONAL STUDY		
S. No:	Date:	
Patients Name:	Age:	Sex: Male/Female
Drugs Prescribed (Name, Dose, Dosage Form):		
No of FDCs:	No of API:	
No of FDC prescribed in generic name:		No of FDC prescribed in brand name:

S. No	**Rationality Criteria**	**Yes (1)**	**No (0)**
1	API from NLEM and WHO EML		
2	Dose of API appropriate for intended use		
3	Proportion of API appropriate for intended use		
4	API should have different mechanism of action		
5	PK and PD interaction		
6	FDC facilitate dose reduction of API		
7	FDC facilitate adverse drug reaction		

REMARKS

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NATIONAL HOSPITAL

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CERTIFICATE

This is certify that the dissertation work entitled "**CURRENT PRESCRIBING TRENDS AND RATIONALITY OF FIXED DOSE COMBINATIONS IN A SOUTH INDIAN MULTI SPECIALITY HOSPITAL"** is the bonafide work carried out by **Mr. SREEHARI K (REG NO. 261940564)** Department of pharmacy practice, **JKK MUNIRAJAH MEDICAL RESEARCH FOUNDATION, COLLEGE OF PHARMACY,** Komarapalayam, under my supervision, Duration between NOVEMBER 2021 TO FEBRUARY 2022.

This is forwarded to the Tamilnadu Dr.M.G.R. Medical University, Chennai in the Partial fulfillment of requirements for the degree of Master of pharmacy in pharmacy practice.

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