

# Rational *Drugs*



An Update on Rational Drug Use

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## REVIEW TOPIC

# FIXED DOSE COMBINATIONS (FDCs)

### THE SCIENCE

Recently, in India Fixed Dose Combination (FDC) of drugs/medicines has drawn the attention of health service providers and the service recipients.

A **fixed dose combination (FDC)** is a formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses. Fixed dose combination drug products may improve medication compliance of patients. Fixed dose combination drugs are also developed to target a single disease like AIDS, TB and malaria.

Some of the FDCs are reviewed by the FDA and the active ingredients used therein are not expected to interact adversely with each other, but may interact with other drugs that a patient is taking. Though FDCs may reduce burden of consuming more pills, there are some disadvantages. Like, if a patient needs dosage adjustment, the existing FDC may not suit the most appropriate strength for the patient. Further, after using an FDC if an adverse drug reaction occurs, it may be difficult to identify the active ingredient responsible for causing the reaction.

A pharmaceutical company may develop a FDC with the sole aim of marketing advantage of exclusive rights to sell the FDC, even though the individual active ingredients may be off-patent. When more than two drugs are combined, the cumulative toxicity and risk-benefits of the new product need to be examined before marketing such products.

### FDC & INFECTIOUS DISEASES

There is emergence of previously unreported infectious diseases and re-emergence of infectious diseases thought

to be on the way to elimination. There is also evidence of infectious pathogens exhibiting antimicrobial resistance even in multiple-drug usage.

Advantages and disadvantages of fixed-dose combinations by Warren Kaplan

#### Advantages

- ◆ Simpler dosage schedule improves compliance and therefore improves treatment outcomes
- ◆ Reduces inadvertent medication errors
- ◆ Prevents and/or slows attainment of antimicrobial resistance by eliminating monotherapy (i.e., one drug is never by itself in circulation)
- ◆ Allows for synergistic combinations (i.e., trimethoprim/sulfamethoxazole combination allows each drug to selectively interfere with successive steps in bacterial folate metabolism)
- ◆ Eliminates drug shortages by simplifying drug storage and handling, and thus lowers risk of being "out of stock"
- ◆ Only 1 expiry date simplifies dosing (single products may have different expiry dates)
- ◆ Procurement, management and handling of drugs is simplified
- ◆ Lower packing and shipping costs
- ◆ Less expensive than single ingredient drugs
- ◆ Side effects are reduced by using one drug of the combination for this purpose
- ◆ Potential for drug abuse can be minimized by using one drug of the combination for this purpose (i.e., excessive use of the antidiarrheal narcotic diphenoxylate)

FDCs are the current hot topic of deliberations in the pharmaceutical industry, government (as regulators), NGOs and the pharmaceutical trade. Surprisingly, it is not so among the doctors who prescribe the medicines or the patients who consume. Technically, on one hand it increases patient compliance, but on the other hand there are chances of consuming medicines (FDCs available in market in India), more than what is required. It is in this scenario, this article has been developed.

Editor

is discouraged by side effects of atropine in the FDC atropine + diphenoxylate)

### Disadvantages

- ◆ FDCs are (possibly) more expensive than separate tablets
- ◆ Potential quality problems, especially with rifampicin in FDCs for TB, requiring bio-availability testing
- ◆ If a patient is allergic or has a side-effect to 1 component, the FDC must be stopped and replaced by separate tablets
- ◆ Dosing is inflexible and cannot be regulated to patient's needs (each patient has unique characteristics such as weight, age, pharmacogenetics, co-morbidity, that may alter drug metabolism and effect).
- ◆ Incompatible pharmacokinetics is irrational because of different elimination  $\frac{1}{2}$  lives of individual components
- ◆ Reaction of one of the components (e.g., a rash to sulfamethoxazole in cotrimoxazole) may result in patient avoiding the "innocent" trimethoprim in the future
- ◆ Drug interactions may lead to alteration of the therapeutic effect.

According to Warren Kaplan, combinations make therapeutic sense for HIV, TB and malaria, but the evidence for the utility of combinations is still largely circumstantial.

The products should have therapeutic rationale and are safe, to remain in the market. Poly-pills are used in the UK for primary prevention of heart diseases. Multiple components of FDCs can lead to complex issues of IPR access and global IP rules.

### IMPACT OF FDC ON ADHERENCE

There is inverse correlation between the complexity of a drug regimen and medication adherence. (FDC) therapies are hypothesized to enhance compliance by decreasing the number of required pills. A study compared adherence of a FDC of metformin and glyburide to a 2-pill regimen. Adherence was measured by the proportion of days on which a patient had medication. Compared to 2-pill therapy, FDC resulted in increase in patient adherence. *A study by Feng Pan, Ann Arbor & A. Mark Fendrick, University of Michigan, Michael E. Chernew, Harvard Medical School, USA; Journal of General Internal Medicine, Published online February 21, 2008; <http://www.springer-link.com/content/tu117655u107p3793/>*

Fixed dose combinations (FDCs) in TB therapy reduce the number of tablets to be consumed and thereby increase patient compliance with recommended treatment regimens. FDCs play a significant role in preventing the emergence of drug resistance and successful treatment. "Fixed dose combinations for tuberculosis: Lessons learned from clinical, formulation and regulatory perspective", Panchagnula, R., Agrawal, S., Ashokraj, Y., Varma, M., Sateesh, K., Bhardwaj, V., Bedi, S., Gulati, I., Parmar, J., Kaul, C.L., Blomberg, B., Fourie, B., Roscigno, G., Wire, R., Laing, R., Evans, P., Moore, T; *Methods Find Exp Clin Pharmacol* 2004, 26(9): 703; ISSN 0379-0355

In Gaborone, Botswana, government officials and representatives of drug regulatory agencies from 23 nations, the

research-based and generic pharmaceutical industries, public health leaders, health care providers, advocacy groups (including persons living with HIV / AIDS), academia and members of non-governmental organizations held discussions from March 29-31 on the scientific and technical principles for FDCs for use in the treatment of AIDS, tuberculosis and malaria. Combination therapies, either using single drugs administered together, or FDCs are considered by many to be essential to treating these diseases as well as to limiting the development of drug resistance. Among other advantages, FDCs simplify dosing which could result in better patient adherence to therapy. *Joint statement issued regarding principles for fixed-dose combination drug products by the Southern African Development Community (SADC), the United Nations Joint Programme on HIV/AIDS (UNAIDS), the U.S. Department of Health and Human Services (HHS) and the World Health Organization (WHO) on the Scientific and Technical Principles for Fixed-Dose Combination Drug Products; April 8, 2004*

### STAKEHOLDERS

At the cost of health, every body has become a stakeholder, whether producer of drugs, retailer, or regulator and in most of the cases it is beyond the comprehension of the patient. Now who decides about treatment with medicines? Doctor? Pharmaceutical industry? Trader? Government? or Patient? What are FDCs from the perspective of these stakeholders?

### THE MARKET

Fixed Dose Combination Drugs are available in the treatment of cardiovascular diseases, central nervous system, diabetes, infectious diseases (bacterial infections), Helicobacter pylori, gastro intestinal infections, orthopedic conditions, cough & cold, acquired immune deficiency syndrome-AIDS, HIV infection and tuberculosis), psychiatric disorders and respiratory diseases (asthma and chronic obstructive pulmonary disease-COPD). FDCs cover therapeutic groups like anti-pyretic & anti-inflammatory, gastro-intestinal, analgesics, cough & cold preparations, dermatologicals, oral contraceptives, and combination vaccine products. There are also over-the-counter (OTC) and prescription non-systemic fixed-dose combination products. Thus FDCs are there in almost all the major therapeutic groups and are of interest to common man or patient.

### THE PHARMACEUTICAL INDUSTRY

The Confederation of Indian Pharmaceutical Industries (CIPI), moved the Madras high court and received stay orders on DCGI's directive against the 294 FDC drugs categorized into 'absurd, rejected, banned, and under examination'. The CIPI is now willing to withdraw the cases if the DCGI agrees to allow licenses to the 150 FDC drugs which were categorised as 'need further examination'.

There are thousands of FDCs in the market and most of the small scale units have been manufacturing them as their mainstay business. Now the regulators are planning to include many of them as new drugs and give licences to those coming with scientific data. Large number of SSIs survive on combination drugs.

11 FDC drugs with paracetamol are some of the FDCs

that the industry has agreed to withdraw voluntarily from the market.

## THE REGULATOR

Expert technical committee like Drug Technical Advisory Board (DTAB) examines a new drug for its safety and efficacy before initiating any action. The DTAB approved that a large number of FDC drugs comes under the category of rejected, absurd, etc will be banned. The sub-committee will identify the drugs which will be banned. There are nine members in the DTAB sub-committee, all of whom are experts in the field of pharmacology.

## THE LAW

All the drugs falling under the categories of absurd, banned and rejected will be banned under section 26-A of the Drugs & Cosmetic Act. For doing this, DTAB's permission is necessary.

FDCs are considered to be new drugs under Rule 122 (E) (c) of the Drugs & Cosmetics Rules. All new drugs need to be approved by DCGI for marketing in the country after submission of all relevant pre-clinical and clinical trial data.

Rule 71 and 76 which prescribe conditions for grant of license states "To have the approval, in writing, in favour of the applicant to manufacture drugs formulations falling under the purview of new drug as defined in Rule 122 E, from the licensing authority as defined in clause (b) of Rule 21".

FDC is rational or irrational needs an examination as per provisions made in Schedule-Y. The power of examination of an FDC as per Schedule-Y lies with the Licensing Authority notified under section 21(b) i.e. DCGI (India).

## THE ISSUE

- ◆ As per rule, new drugs are approved by the Drugs Controller General India (DCGI). But the number of FDCs approved only by State Licensing Authority - State regulators (SLA) and not the DCGI are about 1,300. These are set for fresh review as per the guidelines of DCGI. At the same time only those cleared by the DCGI between 1971 and 2007 are considered valid.
- ◆ Drugs Consultative Committee (DCC) is a regulatory body under the Health Ministry, constituted under the Drugs and Cosmetics Act, 1940 to provide advice regarding uniform implementation of the Drugs and Cosmetics Act and the Rules throughout the country. During the last DCC meeting held on June 4, 2007 decision was taken by the DCGI for banning and withdrawal of 294 FDCs from the market.
- ◆ Estimated FDC market: Rs. 3,000 to 3,500 crore.
- ◆ DCGI has prepared four separate lists of these FDCs

approved by SLAs, a) drugs that have been banned, b) drugs rejected by the Centre, c) approved by the Centre, and d) cleared only by the State and not the Centre. This is part of the DCGI's exercise of screening.

- ◆ The banned list of FDCs are like painkillers combining paracetamol and anxiety-drug alprazolam or a paracetamol + analgin combination. The rejected list of FDCs include antibiotic combinations like ofloxacin and cefixime or anti-fungal/allergy drug combinations like fluconazole plus cetirizine (tablet). For banned and rejected drugs the process involved is, taking them out of the market and withdrawing manufacturing licences.
- ◆ There are allegations that some pharma companies resort to irrational combinations to avoid price-control.

## SOLUTION

Industry representatives from pharma associations like CIPI, IDMA, SPIC, FOPE, IPA and OPPI met the DCGI, for lifting the restrictions imposed on some of these drugs. Solution depends on the rationality of profiles of these FDCs prepared by a panel headed by Dr R K Sanghavi for the industry and to what extent eminent pharmacologist Dr Y K Gupta along with DCGI Dr Surinder Singh will accept these.

If the current plans are implemented, the number of irrational combination drugs, which need to be banned from the market, would come down and that was the demand of the pharma industry represented by large companies, over the years.

*At the cost of health, every body has become a stakeholder, whether producer of drugs, retailer, or regulator and in most of the cases it is beyond the comprehension of the patient*

## Reference:

- 1) Effect of fixed-dose combination (FDC) drugs on development of clinical antimicrobial resistance: a review paper; Warren Kaplan
- 2) Fixed-Dose Combination Drugs for Leading Diseases Report Provides a Discussion of the History and Advantages of Fixed-Dose Combination Drug Products, Business Wire - May 20, 2008, <http://www.aegis.org/news/BW/2008/BW080524.html>
- 3) Global Library of Women's Medicine [www.glowm.com](http://www.glowm.com)
- 4) Chronicle Pharmabiz, published since 2007
- 5) Fixed-dose combination (FDC) drugs availability and use as a global public health necessity: intellectual property and other legal issues, Warren Kaplan

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# FDC listed in Essential Medicines Model List, March 2007, WHO

According to WHO, the core list of Essential Medicines presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The WHO list of Essential Medicines, indicates that around 6.5% of the medicines listed therein are FDCs. The following are the combinations which WHO acknowledges as therapeutically valid (and by default all other combinations provide no advantage in combining them).

## Local anaesthetics

Lidocaine + Epinephrine (adrenaline)

## Antibacterials, Beta Lactam medicines

Amoxicillin + Clavulanic acid

Imipenem + Cilastatin (Only listed for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug-resistant infection)

## Other antibacterials

Sulfamethoxazole + Trimethoprim

## Antituberculosis medicines

Isoniazid + Ethambutol

Rifampicin + Isoniazid

Rifampicin + Isoniazid + Ethambutol

Rifampicin + Isoniazid + Pyrazinamide

Rifampicin + Isoniazid + Pyrazinamide + Ethambutol

## Antiretrovirals, Protease inhibitors

Lopinavir + Ritonavir (LPV/r)

## Fixed-Dose Combinations

Efavirenz + Emtricitabine + Tenofovir

Emtricitabine + Tenofovir

Stavudine + Lamivudine + Nevirapine

Zidovudine + Lamivudine

Zidovudine + Lamivudine + Nevirapine

## Antimalarial medicines, For curative treatment

Artemether + Lumefantrine

Sulfadoxine + Pyrimethamine (Only in combination with Artesunate 50 mg)

## Anti-pneumocystosis and antitoxoplasmosis medicines

Sulfamethoxazole + Trimethoprim Inj

## Antiparkinsonism Medicines

Levodopa + Carbidopa

## Antianaemia medicines

Ferrous salt + Folic acid

## Dermatological Medicines (topical)

### Antifungal medicines

Benzoic acid + Salicylic acid Ointment or Cream

### Anti-infective medicines

Neomycin Sulfate + Bacitracin Ointment

## Medicines used in diarrhoea, Oral rehydration

Oral Rehydration salts

## Oral hormonal contraceptives

Ethinylestradiol + Levonorgestrel

Ethinylestradiol + Norethisterone

## Injectable hormonal contraceptives

Medroxyprogesterone acetate + Estradiol Cypionate

## Warning

The US Food and Drug Administration sent Warning Letters to Bayer HealthCare concerning two unlawful, OTC Aspirin products - Bayer Women's Low Dose Aspirin + Calcium (Bayer Women's) and Bayer Aspirin with Heart Advantage (Bayer Heart Advantage). Bayer Heart Advantage combines aspirin and phytosterols in a single tablet. Bayer Women's combines aspirin and calcium carbonate in a single tablet. The products are labelled as being a combination of a drug and a dietary supplement, but when a drug and a dietary supplement are combined in a single tablet, the product is regulated by FDA as a drug. The products, which contain aspirin with either phytosterols or calcium, are unapproved new drugs that require an approved new drug application in order to be legally marketed. Under the OTC drug monograph system, FDA allows some drugs to be marketed without first obtaining agency approval. These drugs must comply with applicable monographs, that is, regulations that set requirements for the drugs' labelling and formulation, as well as the indications (uses) for which the drugs can be marketed. For these two products, labels lacks adequate directions for use by consumers and labels do not have adequate warnings and are misleading.

Source: Chronicle Pharmabiz

## Combination drug for malaria

Growing incidence of drug resistance to the mono therapy for malaria in India, the WHO is for phasing out mono therapy for malaria and introduction of ACT (Artesunate-Sulpha-Pyrimethamine) combination therapy which has worldwide acceptance. According to National Institute of Malaria Research (NIMR), of the total malaria cases, 40-50 per cent is estimated to be of P.falciparum. Chloroquine, which is being used as a first line of treatment for malaria cases, has recently been observed to be resistant.

Source: Chronicle Pharmabiz

## Misused drugs

Combination cough syrups like Phensedyl and Corex that contain codeine phosphate and are considered to be misused as substitute for alcohol. Estimated at about 20 to 25 per cent of this prescription drug is misused, according to market information. In North and north-eastern states including Uttar Pradesh and Assam where these products are in high demand off prescription are sold in much higher price than the printed maximum retail price.

# FDCs from analgesics and orthopaedics groups, to be withdrawn from market (formal announcement is to be made)

These are categorized into 6 groups.

## **a) Banned**

1. analgin + dextropropoxyphene,
2. analgin + diazepam,
3. analgin + diazepam + diphenhydramine,
4. analgin + diazepam + paracetamol,
5. analgin + diazepam + propylene glycol,
6. analgin + dicyclomine + diazepam,
7. analgin + dihydrocethaverine chloride,
8. analgin + ketoprofen,
9. analgin + KET-P-pipereth-o-carb M,
10. dicyclomine + paracetamol + analgin,
11. fempiverinium bromide + analgin + pitofenone hydrochloride,
12. ibuprofen + paracetamol + oxyphenbutazone + phenylisopropyl pyrazolon,
13. mebeverine + alprazolam,
14. paracetamol + alprazolam,
15. paracetamol + analgin,
16. chlorzoxazone + ibuprofen + paracetamol + diclofenac + oxyphenbutazone + magnesium hydroxide;
17. dicyclomine + paracetamol + byrazolon + phenylisopropyl.

## **b) Absurd**

1. activated charcoal + fungal diastase + lactic acid,
2. allobarbitone + phosphodimethyl-isopropyl-pyrazolone,
3. artesunate + arteether + artemether,
4. chlorzoxazone + paracetamol + ibuprofen + diclofenac sodium,
5. norfloxacin + tinidazole + loperamide,
6. paracetamol + diclofenac sodium + cloxacillin + pantoprazole + lactic acid bacillus + serratiopeptidase,
7. paracetamol + diclofenac sodium + magnesium trisilicate + chlorpheniramine maleate,
8. and ranitidine + omeprazole.

## **c) Could be discontinued**

1. 5-bromosalicyl-4chloranilide + salicylic acid,
2. atorvastatin + acetyl salicylic acid + caffeine,
3. chlormezanone + paracetamol + diclofenac sodium,
4. chlomezanone + paracetamol + ibuprofen,
5. ciprofloxacin + tinidazole + dicyclomine,
6. diclofenac + paracetamol + chlormezanone,
7. dicyclomine + dextromethorphan + paracetamol,
8. dicyclomine + paracetamol + chlordiazepoxide,
9. dicyclomine + serratiopeptidase,
10. ibuprofen + colchicines,
11. ibuprofen + paracetamol + colchicines,
12. ibuprofen + paracetamol + magnesium trisilicate,
13. ibuprofen + paracetamol + magnesium trisilicate,
14. mecobalamine + methenamine mandelate,
15. norfloxacin + tinidazole + dicyclomine,
16. ondansetron + paracetamol,
17. ranitidine + cisapride,
18. ranitidine + dicyclomine + clindidium bromide.

## **d) Duplicate FDCs**

1. amoxicillin + clavulanic acid + lactobacillus,
2. amoxicillin + cloxacillin + lactic acid bacillus,

3. amoxicillin + cloxacillin + lacto acid bacillus,
4. amoxicillin + lactobacillus,
5. amoxicillin + lactobacillus acidophilus,
6. amoxicillin + lactobacillus acidophilus + clavulanic acid,
7. atorvastatin + acetyl salicylic acid,
8. cefixime + ambroxol + lactic acid bacillus,
9. cefixime + lactic acid + ambroxol,
10. cefixime + lactobacillus acidophilus,
11. cefixime + lactobacillus acidophilus + ambroxol,
12. cefixime + lactobacillus acidophilus,
13. cefpodoxime + lactic acid bacillus,
14. cefpodoxime + lactic acid bacillus,
15. cefpodoxime + lactobacillus,
16. cefpodoxime + cloxacillin + lactic acid bacillus,
17. diclofenac sodium + serratiopeptidase,
18. diclofenac + paracetamol + chlorzoxazone,
19. diclofenac + serratiopeptidase,
20. diclofenac + serratiopeptidase + paracetamol,
21. diclofenac sodium + serratiopeptidase,
22. diclofenac + serratiopeptidase,
23. dicyclomine + paracetamol + dimethylpolysiloxane,
24. fempiverinium hydroxide bromide + diclofenac sodium + pitofenone hydrochloride,
25. glucosamine + chondroitin + Vit C + Vit - E + manganese sulphate,
26. ibuprofen + paracetamol + dextropropoxyphene,
27. losartan + hydrochlorothiazide + atenolol,
28. losartan + hydrochlorothiazide + ramipril,
29. paracetamol + diclofenac + chlorzoxazone,
30. tiznidine + diclofenac sodium + paracetamol,
31. tramadol + paracetamol + domperidone.

## **e) Though Approved by DCGI Earlier**

1. atorvastatin + aspirin,
2. atorvastatin + ramipril,
3. benfotiamine + pyridoxine + mecobalamine + iositol + alpha lipoic acid,
4. diclofenac sodium + rabeprazole,
5. diclofenac + methyl salicylate + linoleic acid + menthol,
6. diclofenac + rabeprazole,
7. levocetirizine + montelukast,
8. levofloxacin + ambroxol,
9. mecobalamine + alpha lipoic acid + folic acid + vit-B6 + choline,
10. mecobalamine + alpha lipoic acid,
11. mecobalamine + alpha lipoic acid + folic acid,
12. mecobalamine + alpha liopic acid + Vit B1 + folic acid,
13. mecobalamine + calcium pantothenate,
14. mecobalamine + biotine,
15. mecobalamine + carotenoid + alpha lipoic acid + chromium + Vit-B1 + Vit-B complex,
16. mecobalamine + folic acid,
17. mecobalamine + Vit-A + Vit E + Vit-c + Vit B1 + Vit-B6 + Vit-D3 + selenium,
18. mecobalamine + vitamins + minerals,
19. mecobalamine + Vit-B1 + Vit-B2 + vit-B6 + folic acid,
20. mecobalamine + Vit -B1 + Vit -B6 + folic acid + alpha lipoic acid,
21. mecobalamine + Vit -B1 + Vit -B6 + nicotinamide + D-panthenol,
22. mecobalamine + Vit-B6 + folic acid.

# Drug Information, WHO

It is important and relevant to understand information on every drug/medicine before combination of drugs are prescribed. The WHO South East Asia Regional Office has organized the First Inter-country Workshop on National Drug Information Services at Chennai from May 8 - 11, 2007.

Pharmacists and doctors from Bhutan, India, Maldives, Nepal, and Sri Lanka participated in the workshop. The Regional Adviser, Essential Drugs and Medicines WHO, Regional Office for South-East Asia (SEARO) Dr K Weerasuriya, delivered the message from Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia Region.

Quote from Dr Plianbangchang: "Medicines are a commodity that is subject to market forces; it is a highly profitable commodity producing a high rate of return. It is therefore understandable why those involved in its production and sale would try to influence the decision as to what medicines are prescribed and sold". He further elaborated that "when information on medicines is looked at from the perspective of health, there should be only one objective – information to prescribe the correct medicine using the generic name, in the correct dose, for the correct duration with affordability in mind, and with the appropriate information being provided to the patient or consumer. To achieve this, drug information should be evidence based, scientifically driven and unbiased. Scientific literature, which should be the basis for this evidence, should be specified as a part of transparency".

Some of the Web Sites listed on Drug Information are,

## General

MED-E-SERV <http://www.medeserv.com.au/>  
Medical dictionary <http://cancerweb.ncl.ac.uk/omd/>  
MedicinesComplete <http://www.medicinescomplete.com/mc/>  
Medscape <http://www.medscape.com/>  
National Prescribing Curriculum <http://nps.unisa.edu.au/new/index.htm>  
National Prescribing Service <http://www.nps.org.au/>  
UK Medicines Information <http://www.ukmi.nhs.uk/>  
US FDA - CDER <http://www.fda.gov/cder/>

## Clinical Guidelines

AIDSinfo - HIV-AIDS (US) <http://www.aidsinfo.nih.gov/>  
Australian Skeptics <http://www.skeptics.com.au/>  
CADTH (Canada) <http://www.ccohta.ca/>  
CRISP (NIH) <http://crisp.cit.nih.gov/>  
Centre for Evidence-Based Medicine <http://www.cebm.net/>  
Evidence-Based On-Call (UK) <http://www.eboncall.co.uk/>  
National Center for Complimentary and Alternative Medicine <http://nccam.nih.gov/>  
National Prescribing Centre (UK) <http://www.npc.co.uk/>

National electronic Library for Health (NeLH) <http://www.nelh.nhs.uk/>  
NeLH - Guidelines Finder <http://rms.nelh.nhs.uk/guidelinesfinder/>  
Prodigy Guidance List (UK) <http://www.prodigy.nhs.uk/>  
Scottish Medicines Consortium <http://www.scottish-medicines.org.uk/>

## Drug Compendia

AHFS Drug Information <http://www.ashp.org/ahfs/>  
Australian Medicines Handbook <http://www.amh.net.au/>  
British National Formulary <http://bnf.org/>  
German drugs Rote Liste <http://www.rote-liste.de/>  
Hollings Pharmacy, NZ file: <http://F:/Data/Druginfo/Hollings%20Pharmacy,%20NZ.htm>  
Japan Pharmaceutical Reference <http://www.e-search.ne.jp/~jpr/>  
New Drugs or Indications <http://www.pslgroup.com/NEWDRUGS.HTM>  
New Zealand Medicines Authority <http://www.med-safe.govt.nz/>  
Singapore CDA [http://www.hsa.gov.sg/html/cda/about\\_cda.html](http://www.hsa.gov.sg/html/cda/about_cda.html)  
Therapeutic Guidelines <http://www.tg.com.au/>  
UK drug data sheets <http://emc.medicines.org.uk/>  
WHO Essential Drugs <http://www.who.int/medicines/>

## Health Care Sites

All India Drug Action Network <http://www.aidanindia.org/>  
Centers for Disease Control and Prevention (US) <http://www.cdc.gov/>  
E-drug <http://www.essentialdrugs.org/>  
International Network for Rational Use of Drugs <http://www.msh.org/inrud/index.html>  
Medicines Control Agency (UK) <http://www.mca.gov.uk/>  
National Prescribing Centre (UK) <http://www.npc.co.uk/>  
Therapeutic Guidelines <http://www.tg.com.au/>  
WHO - Uppsala Monitoring Centre (for ADRs) <http://www.who-umc.org/>  
WHO drug stats ATCs <http://www.whocc.no/atcddd/>

## Interactions

CYP interactions (Flockhart) <http://medicine.iupui.edu/flockhart/>  
HIV Drug Interactions <http://www.hiv-druginteractions.org/>  
HIV i-Base Interactions <http://www.i-base.org.uk/>

Source: SEA-Drugs-156, SEARO, WHO, New Delhi, February 2008

## NEW DRUGS

Though a number of combination formulations are approved by the Drugs Controller General India, for the prescriber it is the rationality of use that matters in practice. The following is the list of new drugs approved by the Drugs Controller General (India) from 30<sup>th</sup> August 2006 onwards. In the previous issue we had published the new drugs approved upto August 29, 2006.

Sl. No.	Name of Drug	Indication	Date of Approval
1	S(-) pantoprazole (as sodium) 20mg (E.C.) + Domperidone SR 30mg tablet	FOR GERD	30.08.06
2	Cefadroxil 500mg + Clavulanic acid 125mg tablet	Antibiotic	30.08.06
3	Cefadroxil 250mg + Clavulanic acid 62.5mg dispersible tablet	Antibiotic	30.08.06
4	Cefadroxil 250mg + Clavulanic acid 62.5mg per 5ml syrup	Antibiotic	30.08.06
5	Human Insulin (r-DNA) Powder inhaler	For type-I & Type-2 Diabetes	30.08.06
6	Fulvestrant Inj. 250mg/5ml prefilled syringe	Anti Cancer	30.08.06
7	S(-) Pantoprazole (as Sodium) Inj. 20mg/vial	For peptic ulcer, GERD & Zollinger Ellison Syndrome	30.08.06
8	Dasatinib tablet 20mg/50mg/70mg tablet	For chronic hepatitis B infection	30.08.06
9	Telbivudine 600mg tablet	For chronic hepatitis B infection	30.08.06
10	Aprepitant cap (80mg/125mg)	For chemotherapy induced nausea & vomiting	30.08.06
11	Telmisartan 40mg + Amlodipine (as Besylate) 5mg tablet	For essential hypertension	30.08.06
12	Gemifloxacin (as mesylate) 320mg tablet	Antibiotic	30.08.06
13	Ceftazidime 500mg /1000mg + Tazobactam (as sodium) 62.5mg/125mg per vial for injection	Antibiotic	30.08.06
14	Cefepime (As Hcl) 500mg/1000mg + Tazobactam (as Sodium) 62.5mg/125mg	Antibiotic	30.08.06
15	Paromomycin Inj. 375mg/ml	For visceral leishmaniasis (Kalaazar)	30.08.06
16	Cefixime 100mg + Cloxacillin (as Sodium) 500mg + Lactobacillus (45 million spore) tab.	Antibiotic	31.08.06
17	Alprazolam Dispersible Tab. 0.125mg/0.25mg/ 0.50mg	For anxiety	20.09.06
18	Epinastine Hcl 0.05% Ophthalmic solution	For allergic conjunctivitis	22.09.06
19	Levofloxacin tablet 250mg /500mg & Infusion 5mg/ml (For additional indication)	For prostatitis	26.09.06
20	Feracrylum 1% mouth gargle 10mg/ml	As haemostatic agent in dental surgery	28.09.06
21	Aceclofenac Inj. 150mg/ml	For pain in post operative & post traumatic cases	28.09.06
22	Formoterol fumarate 6mcg + Fluticasone propionate 50mcg/125mcg/250mcg MDI	For Asthma & COPD	14.10.06
23	Amlodipine 25mg + Metoprolol 25mg (additional lower strength)	Anti hypertensive	01.11.06
24	Estrogen vaginal tablet 25mcg	For atrophic vaginitis	02.11.06
25	Esomeprazole 40mg (E.C.) + Itopride 150mg SR Capsules	For GERD	13.11.06
26	Cefixime 200mg + Cloxacillin 500mg (ER) + Lactobacillus 90 million Spore tab. (additional strength)	Antibiotic	14.11.06
27	Cefixime dispersible tablet 400mg (new dosage formulation)	Antibiotic	22.11.06
28	Trandolopril 1mg/2mg/4mg/2mg + Verapamil (ER) 240mg/240mg/240mg/180mg	Anti hypertensive	23.11.06
29	Ciclesonide 160mcg/320mcg cap. for inhalation	Anti asthmatic	28.11.06
30	Rabeprazole 20mg (EC) + Itopride SR 150mg	For GERD	28.11.06
31	Metoprolol succinate 25mg /50mg ER + HCTZ 12.5mg	Anti hypertensive	30.11.06

**Andhra Pradesh:** The Ministry of Hospital Services, which supplies medicines to the government hospitals, and the Women and Child Welfare Department has already stopped purchasing these 'irrational drugs' already.

**Karnataka:** the SLA has already withdrawn licences of two irrational combination drugs

**Source: Chronicle Pharmabiz**

## National Rural Health Mission (NRHM)

NRHM primarily aims to decentralise the public healthcare system in rural areas. The Mission, besides other goals, attempts to address long standing issues of the health system including poor management of resources, centralized decision making, inadequate financing, *irregular supplies of drugs* (access to medicines) and equipments, unacceptable level of absenteeism, corruption, absence of performance based monitoring, inadequate accountability, wanting HRD policies, fragmented and overlapping policies and programmes and inadequate participation of the private sector. Hence, the Centre is of the view that the district-wise action plans will be more effective. Every district will have a comprehensive action plan charting the immunisation programmes, health schemes covering drinking water, sanitation and nutrition, capacity building and funds allocation for welfare schemes.

Rs 884.06 crores has been allocated during 2007-08 for National disease control programmes including vector-borne diseases, TB, trachoma and blindness, iodine deficiency disorders, integrated disease surveillance and drug addiction control programmes. Other programmes related to contraception, reproductive and child health, pulse polio immunisation, family welfare schemes and population control programmes, are also part of NRHM. The State Governments have been asked to prepare Integrated District Health Action plans.

- ◆ The allocation for the NRHM has been increased from Rs 81.4 billion in 2006-07 to Rs 108.9 billion in 2007-08
- ◆ Number of sub-centres provided with untied funds to tackle contingencies – 1,41,000
- ◆ Number of community health Centres identified for upgradation to Indian Public Health Standards – 2,045 of the 3,220 CHCs
- ◆ Number of health facilities already established patient welfare committees (Rogi Kalyan Samities) – 10,000
- ◆ Appointment on contract basis to fill critical manpower gaps in the public health care facilities – 200,000 doctors, 12,000 midwives, 7,500 staff nurses and 1,200 paramedics
- ◆ Number of Village Health and Sanitation Committees constituted – 1,000,000
- ◆ School health programmes initiated across large part of the country

## An invitation

*Readers are invited to share/send ADR & Pharmacovigilance related problems observed/experienced with details of the concerned product.*

*The focus theme for the next issue will be on 'Treatment of common skin conditions'. We welcome readers to contribute. The future issues will be on, Drug Food interactions – Timing & precautions, Treatment of Diabetes, Treatment of Asthma, Use of non-allopathic medicines.*

## Rational Drugs

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