Report of the Core-Committee for

Revision of

National List of Essential Medicines

November 2015

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Executive Summary

- The Core-Committee was constituted by the Ministry of Health & Family Welfare (MOHFW), Government of India, under the chairmanship of Dr VM Katoch, the then Secretary, Department of Health Research (DHR) and Director General, Indian Council of Medical Research (ICMR), and Dr YK Gupta, Professor and Head, Department of Pharmacology, All India Institute of Medical Sciences (AIIMS) as the Vice Chairman.
- The Core-Committee in its initial meetings deliberated and decided on the criteria for inclusion and deletion of medicines in National List of Essential Medicines (NLEM).
- The criteria for inclusion of a medicine in NLEM are as follows:
  - The medicine should be approved/licensed in India.
  - The medicine should be useful in disease which is a public health problem in India.
  - The medicine should have proven efficacy and safety profile based on valid scientific evidence.
  - The medicine should be cost effective.
  - The medicine should be aligned with the current treatment guidelines for the disease.
  - The medicine should be stable under the storage conditions in India.
  - 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, cost-effectiveness.

  - Price of total treatment to be considered and not the unit price of a medicine.
  - Fixed Dose Combinations (FDCs) are generally not included unless the combination has unequivocally proven advantage over individual ingredients administered separately, in terms of increasing efficacy, reducing adverse effects and/or improving compliance.
  - The listing of medicine in NLEM is based according to the level of health care, i.e. Primary (P), Secondary (S) and Tertiary (T) because the treatment facilities, training, experience and availability of health care personnel differ at these levels.
- The criteria for deletion of a medicine from NLEM is as follows:
  - The medicine has been banned in India.
  - There are reports of concerns on the safety profile of a medicine.
  - A medicine with better efficacy or favorable safety profiles and better cost-effectiveness is now available.
  - The disease burden for which a medicine is indicated is no longer a national health concern in India.
  - In case of antimicrobials, if the resistance pattern has rendered a medicine ineffective in Indian context.
- A Source Document containing list of medicines with its dosage forms, strengths; information regarding their presence in NLEM 2011, NFI 2011, WHO EML 2013 (later updated to include WHO EML 2015); as well specific information on efficacy and safety was prepared in a three day workshop which was used for consultation meetings.

- The Core-Committee through a series of meetings and consultations across the country, deliberated and revised the National List of Essential Medicines (NLEM) 2011.
- Following are the salient features of NLEM 2015:
  - There were 348 medicines listed in NLEM 2011. A total of 106 medicines have been added, and 70 medicines have been deleted to prepare NLEM 2015 which now contains a total of 376 medicines.
  - The apparent mismatch in the total number of medicines will be clear by noticing the following points,
  - In NLEM 2011--
    - Prednisolone was counted as 3 items (prednisolone, prednisolone acetate and prednisolone sodium phosphate),
    - Lignocaine was counted as 2 items (lignocaine and lignocaine hydrochloride),
    - Glucose was counted as 2 items (glucose and dextrose 25%),
    - Gentian violet was counted as 2 items (Gentian violet and methylrosalinium chloride)
    - Sodium chloride was counted as 3 items (normal saline, N/2 saline and N/5 saline)
    - Betamethasone was counted as 2 items (Betamethasone and betamethasone dipropionate)
    - Snake venom antiserum was counted as 2 item (Polyvalent antisnake venom and Specific antisnake venom)
    - Isosorbide mononitrate and isosorbide dinitrate were counted as 1 item.

- Following the direction from Hon'ble High Court of Delhi in the Writ Petition No 1772 of 2015, the core committee was asked to look into the matter of coronary stents (Order from Department of Health and Family Welfare (DFQC section), Ministry of Health and Family Welfare, Government of India; Order No 12-01/Essential Medicines/08-DC/DFQC (FTS-15015) dated 15.10.15). The same is being examined by the committee with experts and a supplementary report will be submitted in due course.
- Medicines in NLEM are listed with reference to the levels of healthcare, namely, Primary (P), Secondary (S) and Tertiary (T). There are 209 medicine formulations listed for all levels of health care (P, S, T), 115 medicine formulations for secondary and tertiary levels (S, T) and 79 medicine formulations for the tertiary level (T).
    - It is to be noted that formulations of certain medicines are listed at different levels but as item, they are counted as one. The total number of medicines remains 376.
- The essentiality of a medicine has been considered in terms of its dosage form and strength also.
- Any dosage form of a medicine, other than the dosage form included in NLEM, but in same strength and route of administration, which does not have significant difference in terms of pharmacokinetics/ pharmacodynamics/ efficacy-safety profile over the dosage form mentioned in the list will be considered as included. To elaborate, if a tablet is included, other dosage forms like conventional tablets and capsules are considered as included. However, such different dosage forms should be considered differently for purposes such as

procurement policy, pricing etc. This principle also applies to all other dosage forms e.g. oral liquid dosage forms, injectables, topical dosage forms etc.

- For listing of oral solid dosage form (tablet/capsule) of medicines in NLEM, two aspects were considered viz dosage form that is commonly available and dosage form that is mentioned in Indian Pharmacopoeia (IP). However, availability has been given priority in this regard.
- Innovation in medicine must be encouraged. The formulations developed through incremental innovation/ novel drug delivery systems like lipid/liposomal formulations, sustained release/controlled release etc. should be considered as included **only if** specified in the list against any medicine. Such different formulations should be considered differently for purposes such as procurement policy, pricing etc.
- In cases, where vaccines/ immunoglobulins/ sera are listed in NLEM, irrespective of variation in source, composition and strength, all the products of the same vaccines/ immunoglobulins/ sera as approved by the licensing authority are considered included.
- In general, medicines have been mentioned with respect to their active moieties, without mentioning the salts. However, in cases where there is significant difference between the salts, the medicine finds mention as its specific salt.
- In cases where an active moiety is available as different isomers/ analogues/ derivatives, they are considered as separate entities, and inclusion of one does not imply inclusion of all isomers/ analogues/ derivatives.

- For injectable preparations, the Pack Size (single and multi-dose packs) has not been mentioned. It is suggested that the single and multi-dose pack sizes be considered as separate entities for purposes such as procurement/ pricing etc.
- In general, Fixed Dose Combinations (FDCs) have not been included unless, the combination has unequivocally proven advantage over individual ingredients administered separately, in terms of increasing efficacy, reducing adverse effects and/or improving compliance.
- The medicines in various National Health Programmes have been considered for inclusion in NLEM. Any medicine/ vaccine, as and when recommended under a National Health Programme will be deemed to have been included in NLEM.
- Over 50 representations, from Pharmaceutical Industries, Associations/ Bodies, NGO's, Ministries were received. After deliberations on each, wherever considered appropriate, the viewpoints have been included.

- The NLEM 2015 has been prepared adhering to the basic principles of Efficacy, Safety, Cost-Effectiveness; consideration of diseases as public health problems in India. The list could be called as a Best-Fit List.

- The number of medicines deleted and added to NLEM 2011, along with number of medicines in NLEM 2015 is given below:

Section	Therapeutic category	Total in NLEM 2011	Deleted	Added	Total in NLEM 2015
1	Anesthetic agents	18	3	1	16
2	Analgesics, antipyretics, nonsteroidal anti-inflammatory medicines, medicines used to treat gout and disease modifying agents used in rheumatoid disorders	14	0	1	15
3	Antiallergics and medicines used in anaphylaxis	9	2	0	7
4	Antidotes and other substances used in poisonings	14	1	1	14
5	Anticonvulsants/ Antiepileptics	7	0	2	9
6.1	Anthelminthics	4	1	1	4
6.2	Anti-bacterial medicines	21	4	5	22
6.2.3	Antileprosy medicines	3	0	0	3
6.2.4	Antituberculosis medicines	6	1	9	14
6.3	Anti-fungal medicines	5	0	0	5
6.4	Antiviral medicines	15	6	14	23
6.5	Antiprotozoal medicines	15	4	4	15
7	Antimigraine medicines	4	1	2	5
8	Antineoplastic, immunosuppressives and medicines used in palliative care	40	6	25	59
9	Antiparkinsonism medicines	3	1	0	2
10	Medicines affecting blood	10	3	6	13
11	Blood products and plasma substitutes	10	4	2	8
12	Cardiovascular medicines*	29	5	5	30
13	Medicines used in dementia	NA	NA	1	1
14	Dermatological medicines	16	6	5	15
15	Diagnostic agents	11	6	2	7

Section	Therapeutic category	Total in NLEM 2011	Deleted	Added	Total in NLEM 2015
16	Dialysis solution	1	0	1	2
17	Disinfectants and antiseptics	12	3	0	9
18	Diuretics	4	0	0	4
19	Ear, nose, throat medicines	NA	NA	4	4
20	Gastrointestinal medicines	16	3	3	16
21	Hormones, other endocrine medicines and contraceptives	24	4	3	23
22	Immunologicals	13	0	4	17
23	Muscle relaxants and cholinesterase Inhibitors	5	1	1	5
24	Medicines used in neonatal care	NA	NA	3	3
25	Ophthalmological medicines*	17	5	6	17
26	Oxytocics and antioxytocics	7	1	1	7
27	Psychotherapeutics	11	5	7	13
28	Medicines acting on the respiratory tract	6	3	3	6
29	Solutions correcting water, electrolyte and acid-base disturbances*	10	0	0	8
30	Vitamins and Minerals	10	2	1	9

* Total number of medicines may differ due to duplication of medicines within and across therapeutic categories/ difference in terms used in NLEM 2011 and NLEM 2015

Report of the Core-Committee for Revision of National List of Essential Medicines

During recent years, the National List of Essential Medicines (NLEM) of India has assumed immense importance in minds of users and government. This has mainly resulted from various policy initiatives of the government to improve access to medicines in India. It is therefore important to understand the history of preparing the list of essential medicines in India and other international agencies like the World Health Organization (WHO); evolution of these processes; and concepts and principles being applied to prepare and use of such lists. This will help the user to adopt transparent and justified procedures wherever they find usefulness of this list.

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. The table below displays the number of medicines in WHO EML and NLEM over the years:

Year	WHO EML	NLEM
1977	204	-
1979	235	-
1983	243	-
1985	263	-
1988	280	-
1990	293	-
1992	300	-
1995	301	-
1996	-	279
1997	310	-

Year	WHO EML	NLEM
1998	317	-
2000	322	-
2002	341	-
2003	331	354
2005	319	-
2007	337	-
2009	352	-
2011	358	348
2013	374	-
2015	414	376

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 middle-income 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.

Considerations for Framing the NLEM 2015

Essentiality

Every medicine may be necessary or even critical for specific disease conditions for which it is indicated. But in the context of NLEM, a medicine may be essential considering the population at large and should fit into the definition mentioned earlier. Hence, a medicine which is critical for a specific condition may not be listed in the list of essential medicines if the disease condition for which it is indicated has low prevalence or is rare. This does not mean that if a particular medicine is not included in the list of essential medicines, it is not necessary. In no way, exclusion of such medicines from the list undermines their importance in therapeutics and need of their availability at an affordable cost.

Some examples are:

a. Imiglucerase, the only definitive treatment of Gaucher's disease, a rare inborn error of metabolism, doesn't find a place in the list
b. Spiramycin is the only treatment available for the prevention of vertical transmission of *Toxoplasma gondii* infection. However, Toxoplasma is not a priority health care need of the country and hence spiramycin is not an essential medicine in the Indian context
c. Desmopressin is the only medicine for Diabetes Insipidus but because of the rarity of the condition it may not find a place in the NLEM

The NLEM can serve as a reference document for medicines of national importance so that administrative, scientific, pharmaceutical and logistic

efforts are appropriately directed leading to optimum utilization of the resources available for effective healthcare delivery.

Changing Disease Burden

Disease burden is an important consideration for identifying the essential medicines. Medicines needed to manage diseases that are highly prevalent or are emerging diseases in the population will qualify for inclusion in the NLEM. For example, MDR tuberculosis is increasing in incidence and is a public health issue. Similar is the case with increasing prevalence of resistant malaria. These necessitate the inclusion of medicines in NLEM to address the above issues.

Efficacy and Safety

Safety and efficacy are the most important criteria for considering essentiality of a medicine. For a medicine to be considered essential, it should have an unequivocal evidence of efficacy and wider acceptance in medical science. The medicine should have a safety profile which is acceptable in terms of risk benefit assessment. The safety profile of a medicine may change over time as new adverse effects may be discovered after wider use of the drug. This may change the risk benefit assessment and a drug once preferred may no longer remain so. For example, pioglitazone is an effective and cheap antidiabetic drug but it recently came under the scanner because of the safety concern of bladder cancer.

Though the drug finds its use in specific diabetic conditions, the same is with various safety restrictions. Therefore, pioglitazone has not been considered essential in spite of being effective for a specific diabetic condition.

Comparative Cost-effectiveness

This is especially important when selecting more than one medicine from the same therapeutic category and when they do not differ significantly in their efficacy & safety. Sometimes per unit price of the medicine may be more but it may be required to be given at a lesser frequency. Thus the total price of the treatment schedule should be taken into consideration and not the unit price alone.

Feasibility in context of advantage and cost-effectiveness

An essential medicine should be available in a form in which adequate quality throughout its shelf-life under recommended storage conditions is ensured. For example, liquid formulation of antisnake venom is cheaper and equi-efficacious as compared to the lyophilised preparation. However, lyophilisation involves use of technology and cost. Whereas, liquid formulation requires cold chain, which is sometimes difficult to maintain in its distribution channel. Considering the advantage of one and the cost-effectiveness of the other, both lyophilized and liquid formulations have been included in the List. They have been listed as separate items and should be considered differently by the user of NLEM.

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.

Sales Turnover

The sales of a medicine in terms of moving annual total (MAT) volume and MAT value may not be criteria for essentiality. A medicine with high volume of sales may or may not qualify as essential since the sales of a medicine is likely to be impacted by factors such as market forces, physician's preferences, and influences of Key Opinion Leaders etc especially for countries like India where there is lack of universally acceptable treatment guidelines for many disease conditions. For example, several multivitamin preparations such as Vitamin B complex, Vitamin C with minerals like zinc etc are widely consumed and figure very high on the MAT list. But considering the criteria for inclusion in NLEM, these preparations do not qualify for their inclusion. Some FDC which figure very high may not be even rational and need attention of regulator to assess their continued marketing. Such formulations obviously, will not meet the essentiality criteria.

Hierarchy of Health Care Structure

The health care system in India is essentially a three-tier system with primary, secondary and tertiary levels having different health care concerns and medicine requirements. While a primary health care level setup may require medicines prescribed in an outpatient setup like basic antibiotics, analgesics and anti-inflammatory drugs; a tertiary level setup might need more parenteral medicines and medicines used in an inpatient setup.

The health care facility at the primary care center may not be adequate for use of medicines which require special facilities and techniques for their

administration. Therefore, infrastructure at the PHC might preclude use of such medicines. The use of high-end antimicrobials, and medicines for conditions like resistant tuberculosis, malaria, kala-azar; oncology medicines etc will be required more in tertiary care.

Thus, the essentiality of the medicine will also depend upon the hierarchy of the health care system, and hence the need to bucket the essentiality as:

I. (P) = Primary care facility
II. (S) = Secondary care facility and
III. (T) = Tertiary care facility

Building NLEM

It was decided by the Core-Committee that NLEM should be developed through a consultative and transparent process. Considering the health care structure of India, the essential medicines are to be classified targeting the levels of health care facilities namely Primary (P), Secondary(S) and Tertiary (T).

It was decided that the consultation would involve experts of different therapeutic areas across the country. Other stakeholders including pharmaceutical industry, non-government organizations, etc be given an opportunity to express their viewpoint to the Committee.

Unique characteristics of India that makes Indian NLEM different

Patterns of Disease prevalence:

India is the second most populous country in the world. With the improvement in public health care and the socioeconomic status, India faces the twin epidemic of continuing/emerging infectious diseases as well as non-communicable, lifestyle diseases. The temporal landscape of India's health care priorities makes an interesting study.

The country's post-independence period has witnessed a unique trend in disease prevalence. The communicable diseases like small pox, plague, polio, diphtheria, pertussis, tetanus, tuberculosis and vector borne diseases dominated the initial post-independence period. Whereas, the second phase saw a remarkable decline in some of the these communicable diseases and emergence of the non-communicable and lifestyle diseases like diabetes, hypertension, coronary artery disease, cancer, and mental illness and neurodegenerative disorders etc.

The current scenario is unique with an increase in the burden of non-communicable diseases and resurgence of certain communicable diseases either due to emergence of drug resistance, like in tuberculosis and malaria, or occurrence of certain co-infections like HIV and TB, and HIV and sexually transmitted diseases, or due to evolution of the pathogens as in case of influenza like H1N1, dengue etc.

The selection of essential medicines for various therapeutic areas have been considered taking into view the larger perspective of present scenario with regards to disease prevalence in the country.

Health Care Expenditure in India

In India, a substantial part of health expenditure is out of pocket. Most of this expenditure is for outpatient care especially on medicines. The past decade has seen a rise in the public adoption of insurance schemes. Nevertheless, the health insurance schemes are often underutilized in India. Very small subset of the Indian population is covered through health insurance, most of it being government employees and organized sectors.

The most vulnerable groups like workers of unorganized sectors, migrant workers and agriculture dependent population are left out of the insurance coverage and are fully dependent on the out of the pocket spending for

purchase of medicines. Many states are providing free medicine. The NLEM may act as a guidance document for governments to frame strategy in this regard.

NLEM and Related Price Control Issue

In order to make medicines affordable, Government of India promulgated the National Pharmaceutical Pricing Policy, 2012 bringing all medicines with specified dosage and strength included in NLEM under price control. Accordingly, Drug Price Control Order, 2013 was issued by Department of Pharmaceuticals under Ministry of Chemicals and Fertilizers for fixing the ceiling price of medicines included in NLEM, 2011.

The main objective of NLEM is undoubtedly to promote the rational use of medicines and optimum utilization of resources available for health care delivery, however, because of the reasons stated above it has become the reference point for price regulation as well, thereby leading to intense deliberations.

This has often shifted the core focus of discussion in consultation meetings. However, the core committee was successful, though with much efforts, to bring back the centre of discussion to the main theme of efficacy, safety, comparative cost-effectiveness and the prevalence of disease as major criteria for drafting NLEM.

Innovation and NLEM

Considering the huge disease burden in a country like India, research and development is of paramount importance for bringing new medicines into the market. Discovery and development of new medicine molecules is a complex, knowledge intensive activity requiring involvement of expertise from various fields, considerable time and resources.

Indian pharmaceutical industry being strong in manufacture of generic medicines and Novel Drug Delivery Systems (NDDS) should be encouraged for incremental innovations in therapeutics and medicine. The user of NLEM may consider this aspect while using the NLEM for providing services in the health care system.

List of Essential medicines – a Dynamic Document

The list of essential medicines cannot be static but has to be ever dynamic. It needs to be updated/ revised periodically due to the following reasons:-

Changing Disease Burden Profile

The disease burden in a population does not remain static and keeps on changing both in short and long term. Diseases of the elderly such as dementia are fast becoming a public health issue. In the revised NLEM, therefore, medicine for dementia has been added.

Antimicrobial Resistance

Development of resistance for medicines used for treatment of various infections like malaria, TB, HIV, kala-azar etc, have been reported in the country as well as the world. Emergence of resistant pathogens necessitate inclusion of newer antimicrobials for the treatment of such infectious conditions which in turn require update of NLEM regularly. Considering emergence of resistance, many medicines have been included in NLEM 2015.

Development of Newer and Better Medicines

The approval of newer and better medicines results in change in treatment practices/ guidelines for various disease conditions. For example ergot alkaloids (dihydroergotamine) were commonly used for the treatment of acute attack of migraine. However with the introduction of safer

alternatives of 5 HT 1b/d agonists, medicines of this class are now preferred over the existing ones. Among various 5HT 1b/d agonists, sumatriptan has been considered as essential in place of dihydroergotamine.

Similarly, availability of rituximab for NHL has changed the treatment regimen for this disease.

In view of the above, NLEM requires regular revision so as to preserve its relevance. NLEM has been revised twice, the last being in 2011.We recommend the revision at every three years.

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. Copy of the order is annexed as annexure I.

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, cost-effectiveness.
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

Selection of Experts

The Core-Committee decided that in country wide consultations, the experts of different subject domain, representatives of different national health programmes such as Revised National Tuberculosis Control Program (RNTCP), National AIDS Control Program (NACP), and National Vector Borne Disease Control Programme (NVBDCP); will be invited. It was also decided that representatives from industry, and NGOs would be invited to place their viewpoint before the committee.

Accordingly, email was sent to Principals/ Deans of Medical Colleges, to Director of Health Services of various states to nominate experts. In addition, domain experts were also identified from the expert pool of CDSCO and also by the committee based on available information.

Classification of Therapeutic Categories for Consultation by Expert Panels

Committee noted that in NLEM 2011, the medicines were listed in 27 therapeutic categories. For logistic reasons, it was decided to have five expert panels which will cover all therapeutic areas. Accordingly, all the therapeutic categories of medicines were divided into five groups for deliberation by the expert panels in each consultation meeting.

Source document to guide the revision process

The committee noted that there was no comprehensive source of information to give the list of all licensed medicines in the country with their formulations, strengths, dosage forms etc. Further there was no

updated document to provide, at a glance, the important efficacy issues and safety concerns of all medicines.

It was, therefore, decided to prepare a comprehensive Base Document consisting of medicines available in India. The following information was included in the base document

1. List of all medicines of various therapeutic categories with dosage forms and strengths.
2. Information regarding their presence in
    a. NLEM 2011,
    b. National Formulary of India 2011
    c. WHO EML 2013 (later updated to 2015)
3. If the medicine is mentioned in the National Health Programmes of India
4. Some specific information on efficacy and safety issues

For preparing this document, a 3 day workshop was organized on Oct 17-20, 2014 in Delhi. Junior faculty members, senior residents and junior residents of Pharmacology from different Medical Colleges of Delhi and officials of CDSCO participated and deliberated.

The source document was prepared to be placed and projected to various expert panels during consultations to give them available information of the medicines for deliberation and recommendation.

Consultation Meetings

Consultation meetings were held in 6 places across the country. The dates and venue of these consultation meetings are as under:

1. Oct 31-Nov 1, 2014 at National Institute for Research in Reproductive Health, Mumbai
2. Nov 16-17, 2014 at National Institute of Nutrition, Hyderabad

3. Dec 13-14, 2014 at Calcutta School of Tropical Medicine, Kolkata
4. Dec 29-30, 2014 at Gauhati Medical College and Hospital, Guwahati
5. Jan 18-19, 2015 at Bangalore Medical College, Bangalore
6. Feb 18-19, 2015 at All India Institute of Medical Sciences, New Delhi

These consultations were attended by about 350 experts from different disciplines. In each consultation, opportunity was given to the Pharmaceutical Industry and Non-Governmental Organizations through advertisement in the newspapers for expressing their viewpoint.

Orientation of Experts

To reiterate the concept and principles of NLEM, a special session was organized before start of each consultation meeting, highlighting the need for NLEM, its philosophy, principles and practices to be kept in mind while deliberating the matter. Key considerations for framing NLEM 2015 were explained to the experts with the help of real world examples. This was followed by the closed session of subject experts to deliberate on the list.

Transparent Approach in Consultation

The Consultation was conducted in a manner in which transparency, fidelity of inputs and identification of the contributors were ensured. In each consultation meeting, the experts were divided into five panels as per their expertise.

The source document was displayed before the experts for deliberation. Experts were free to give their opinion based on information in the source document as well as any other information based on their clinical experience. Their inputs were recorded on predesigned Performa. Audio/ Audio-visual recording of the proceedings was done with prior knowledge

and permission of participants as per logistics available at different consultation meetings.

Evidence Based Justification of Additions and Deletions

The experts were requested to support their inputs with suitable evidence. If their opinion was based on their clinical judgment and experience, it was recorded as such. Experts were also at liberty to provide evidence even at a later date through mail. More evidence was further generated by the team of rapporteurs and was scrutinized by Core Committee.

Core-committee Meetings – for Deliberation

Following the country wide consultation meetings, the recommendations of the expert panels were compiled by the rapporteurs and presented in a section-wise manner to the Core Committee for further deliberation. The Core-Committee deliberated the matter in meetings held on 17th March, 27th March, 10th April, 22nd April, 8th May, 23rd May, 24th June, 16th July, 4th Sep and 29th Oct in Delhi.

Specific Issues Deliberated during the Revision Process

The following specific dimensions were considered during deliberation:

1. Dosage forms/ formulations
2. Strengths of medicines
3. Salts of active moieties of medicines
4. Isomers/ analogues/ derivatives etc. of medicines
5. Medicines in national health programmes
6. Pack size of formulations
7. Incremental innovation
   I. Formulations of Modified release/ Sustained release/ extended release etc.

II. Improved or novel drug delivery systems

Dosage Forms/ Formulations of a Medicine

Formulation of a medicine may be available in different dosage forms.

Oral solid dosage forms include tablet, capsule, sachet, etc.

Tablets include film coated, uncoated, sugar coated etc.

Capsules include hard gelatin capsule, soft gelatin capsules etc. (Unless specified, capsules mentioned in the NLEM are considered as hard gelatin capsules).

Oral liquid dosage forms include syrup, suspension, elixirs etc.

Injectable dosage forms include conventional liquid injection or powder for injection, as well as delivery system like depot, liposomal/ lipid complex etc.

Topical dosage forms include ointment, cream, lotion, drops etc.

When the solid oral dosage form of the medicine is available both as tablet and capsule, the more commonly available dosage form (between tablet and capsule), is listed in NLEM.

If both the formulations i.e. tablet and capsule are available in almost equal proportions, the formulation as included in Indian Pharmacopoeia, has been listed in NLEM. For example, ibuprofen which is included in IP as tablet, is listed in NLEM as tablet though it is also available as capsule. Similarly, tramadol is mentioned in IP as capsule, but is also available as tablet. In NLEM, it has been listed as capsule.

Where, more than one solid oral dosage form is mentioned in IP, the more commonly used form is listed in NLEM. However, in case the formulation is not mentioned in IP, the more commonly available dosage form is mentioned in NLEM.

Oral liquid formulation may be available as syrups, suspensions, solutions

etc. In NLEM, all such formulations are listed as oral liquid dosage forms.

Similarly, many medicines intended for topical use are available as cream, ointment, lotion etc. If the formulation is included in Indian Pharmacopoeia, the same dosage form as mentioned in IP is listed in NLEM. For example, fusidic acid and silver sulfadiazine, are available as cream and ointment, but only cream is mentioned in IP. Hence, in NLEM they are listed as cream. Where, more than one dosage form is mentioned in IP, the more commonly used form is listed in NLEM. However, in case the medicine is not included in IP, the more commonly available form is mentioned in NLEM.

For pricing and policy decisions, only the similar formulations of oral solid dosage forms should be grouped together. However, if different technology is involved, such different dosage forms may be considered separately by purposes such as pricing, procurement etc. Any dosage form of a medicine, other than the dosage form included in NLEM but in same strength and route of administration, which does not have significant difference in terms of pharmacokinetics/ pharmacodynamics/ efficacy-safety profile over the dosage form mentioned in the list, should be considered as included. To elaborate, if tablet is included, other dosage forms like conventional tablets and capsules are considered as included. However, such different dosage forms should be considered differently for purposes such as procurement policy, pricing etc. This principle also applies to all other dosage forms e.g. oral liquid dosage forms, injectables, topical dosage forms etc.

Biological Medicines

Vaccines, sera and immunoglobulins are complex biological products. There are some vaccines/ sera/ immunoglobulins that may be manufactured from different sources, by using different process and technology.

Therefore, in such cases, irrespective of variation in source, composition or strengths, all the products of the same vaccine/ sera/ immunoglobulin, as approved by licensing authority are considered as included in NLEM. However, considering the source, process, technology and other relevant aspects, different products of the same biological should be considered differently by the user.

Incremental Innovation

The Committee deliberated in detail about the issue of inclusion of improved formulations of a medicine developed through incremental innovation involving technology. The Committee considered that such formulations including novel drug delivery systems like lipid/ liposomal formulations, modified release formulations like sustained release, controlled release etc. of a medicine, which are developed to overcome certain disadvantages associated with the use of conventional formulations, will be considered included **only if** specified in the list against any medicine.

Strengths of a Medicine

Formulations of a medicine are usually available in many strengths. The Committee deliberated that where more than one strength(s) is/ are available, the strength(s) which is/ are appropriate and meet the need of most, have been considered for inclusion in the NLEM.

Some strengths of a particular formulation of some medicines, presently available in the market do not appear to be appropriate and are rarely required. The committee recommends that such strengths may be examined by the regulators in consultation with experts for appropriateness of continuance of such strengths.

Different salts of active moiety of a medicine

The Committee decided that in general, medicines should be mentioned in the NLEM in terms of their active moieties, without mentioning the salts. However, in case, where, the different salts of a medicine have significant difference in potency/ pharmacokinetics/ pharmacodynamics/ efficacy-safety profile, the medicine has been mentioned in the list with respect to its specific salt. The Committee also considered that in case a medicine is available in more than one salt without any significant difference in above aspects, it is implied that all salts of that medicine with specified dosage form and strength are considered included in NLEM, 2015.

For example, diclofenac is available as diclofenac sodium or diclofenac potassium. However there is no significant difference in the above mentioned aspects, between the two salts. Hence only diclofenac is mentioned in the NLEM, which implies that both diclofenac sodium and diclofenac potassium are included in the NLEM.

Isomer/ Analogue/ Derivative of a Medicine

In many cases, different isomers/ analogues/ derivatives of one active moiety are available as different medicines. They may differ with respect to potency/ pharmacokinetics/ pharmacodynamics/ safety-efficacy profile.

For example, S-amlodipine is an optical isomer of amlodipine. These two forms have been considered as separate entities and approved as two different medicines. Therefore inclusion of amlodipine in NLEM does not imply that S-amlodipine is also included in NLEM.

Similarly, oxcarbazepine is a derivative of carbamazepine and both oxcarbazepine and carbamazepine have been considered and licensed as different medicines. Inclusion of carbamazepine in NLEM does not imply that oxcarbazepine is also included.

Thus, wherever, such different forms exist, which have been considered as different entities and licensed as different medicines, inclusion of one form of such medicines in NLEM will not automatically imply inclusion of other forms.

Medicines in Various National Health Programmes

There are several national health programmes in India to address the health care needs in both communicable and non-communicable diseases. The committee deliberated that the medicines recommended in these programmes should be considered for their inclusion in NLEM. The committee acknowledges the fact that the medicines recommended under National Health Programmes keep changing with change in disease prevalence, emergence of drug resistance and availability of newer and better medicines. Any medicine/ vaccine, as and when recommended under a national program the same should be deemed to have been included in NLEM.

Issue of Pack Sizes

It was noted that some injectable preparations are available in single as well as multiple dose packages. Both packaging have their respective relevance for treatment of individual patients and mass programmes. In NLEM the pack size has not been mentioned against the medicines included in the List.

However, the Core-Committee recognizes that for the use of NLEM for different purposes, it should be appropriate to consider the two items as separate, and multiple dose pack sizes should not be considered as simple multiples of single dose pack sizes.

Consideration of representations

The Core-Committee received more than 50 representations from institutions, industry associations, pharmaceutical companies, NGOs, as well as individual experts. The committee considered these representations. Wherever considered appropriate, the viewpoints have been included in the NLEM.

Conclusion

Revision of NLEM has been a complex process in the light of fast changing concepts in medicines, treatment regimens, introduction of new technologies and incremental innovations in drug delivery systems and formulations, wide differences in medical practice pattern in the country, regional variations in health care system etc. Further dimension has been added because of measures of Government to regulate prices of all medicines included in NLEM which has increased the importance of process of revision of NLEM.

The wider consultation with different experts was to understand every body's viewpoint and concerns and deliberate on them. WHO EML was also consulted with respect to the country's need. In the light of the above it was difficult to address all the aspects but the basic principle of EML i.e. efficacy, safety, cost; and consideration of diseases as public health problems in India. The list could be called as a Best Fit list.

Outline of Process of revision of NLEM, 2011

- **Constitution of Core Committee for revision of NLEM 2011**
- Ministry of H&FW Order No. 12-01/13-DC (Pt.98) dated May 7, 2014 to review and revise NLEM 2011
- Chairman: Dr VM Katoch, Secretary, DHR & DG, ICMR
- Vice Chairman: Prof YK Gupta, HOD, Pharmacology, AIIMS, New Delhi
- Core-Committee Members and Subject experts

- **Core-committee meetings to outline the process of revision of NLEM 2011**
- Criteria for inclusion/ deletion of medicine
- Inviting nominations/ identification of experts

- **Decision of holding consultations across the country**
- Categorizing all medicines into 5 groups for consultation by 5 panels in each consultation meeting

- **Preparation of Source Docmuent**
- 3 day workshop of junior faculty and residents from medical colleges from Delhi on October, 17, 18 & 20
- Source document containing information of medicines with dosage forms;strengths; presence in NLEM,WHO EML, NFI; and some specific information about safety and efficacy

- **Consultations (in six cities across the country)**
- Before each consultation, stakeholders invited through newspaper advertisements

- **Dates and venues for consultation meetingss**
- Oct 31-Nov 1, 2014 at National Institute for Research in Reproductive Health, **Mumbai**
- Nov 16-17, 2014 at National Institute of Nutrition, **Hyderabad**,
- Dec 13-14, 2014 at Calcutta School of tropical Medicine, **Kolkata**
- Dec 29-30, 2014 at Guwahati Medical College and Hospital, **Guwahati**
- Jan 18-19, 2015 at Bangalore Medical College, **Bangalore**
- Feb 18-19, 2015 at All India Institute of Medical Sciences, **New Delhi**

- **Deliberations by Core-Committee**
- 17th March, 27th March, 10th April, 22nd April, 8th May and 23rd May, 24th June, 16th July, 4th September, 29th Oct ober 2015