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B.PHARM-PROGRAMME VISION & MISSION

Vision

Striving to excel in pharmaceutical education, research & innovation to develop outstanding professionals catering to the health care needs of the humankind.

Mission

The institute aims to develop employable students, researchers and entrepreneurs by inculcating critical thinking, problem solving ability, ethical values and leadership skills. Institute provides vibrant environment for continuous learning by strengthening industrial collaboration for developing competent professionals.

B.PHARM-PROGRAMME EDUCATIONAL OBJECTIVES

PEO 1: To acquire effective knowledge of pharmaceutical sciences to be able to lead the industry and health care sector

PEO 2: To attain practical training and technical expertise in pharmaceutical sciences

PEO 3: To inculcate professional and ethical standards with effective interpersonal communication skills.

PEO 4: To develop interdisciplinary & holistic approach in Pharmaceuticals for societal cause, problem solving and lifelong learning.

PEO 5: To adapt and implement best practices in the profession by enrichment of knowledge and skills in research and critical thinking.

B.PHARM-PROGRAMME OUTCOMES

No.	Programme Outcomes
PO1	**Pharmacy Knowledge:** Possess knowledge and comprehension of the core and basic knowledge associated with the profession of pharmacy, including biomedical sciences; pharmaceutical sciences; behavioral, social, and administrative pharmacy sciences; and manufacturing practices.
PO2	**Planning Abilities:** Demonstrate effective planning abilities including time management, resource management, delegation skills and organizational skills. Develop and implement plans and organize work to meet deadlines
PO3	**Problem analysis:** Utilize the principles of scientific enquiry, thinking analytically, clearly and critically, while solving problems and making decisions during daily practice. Find, analyze, evaluate and apply information systematically and shall make defensible decisions.

PO4 **Modern tool usage:** Learn, select, and apply appropriate methods and procedures, resources, and modern pharmacy-related computing tools with an understanding of the limitations

PO5 **Leadership skills:** Understand and consider the human reaction to change, motivation issues, leadership and team-building when planning changes required for fulfillment of practice, professional and societal responsibilities. Assume participatory roles as responsible citizens or leadership roles when appropriate to facilitate improvement in health and well-being.

PO6 **Professional Identity:** Understand, analyze and communicate the value of their professional roles in society (e.g. health care professionals, promoters of health, educators, managers, employers, employees).

PO7 **Pharmaceutical Ethics:** Honor personal values and apply ethical principles in professional and social contexts. Demonstrate behavior that recognizes cultural and personal variability in values, communication and lifestyles. Use ethical frameworks; apply ethical principles while making decisions and take responsibility for the outcomes associated with the decisions.

PO8 **Communication:** Communicate effectively with the pharmacy community and with society at large, such as, being able to comprehend and write effective reports, make effective presentations and documentation, and give and receive clear instructions

PO9 **The Pharmacist and society:** Apply reasoning informed by the contextual knowledge to assess societal, health, safety and legal issues and the consequent responsibilities relevant to the professional pharmacy practice

PO10 **Environment and sustainability:** Understand the impact of the professional pharmacy solutions in societal and environmental contexts, and demonstrate the knowledge of, and need for sustainable development.

PO11 **Life-long learning:** Recognize the need for, and have the preparation and ability to engage in independent and life-long learning in the broadest context of technological change. Self-assess and use feedback effectively from others to identify learning needs and to satisfy these needs on an ongoing basis

PO12 **Drugs and diseases:** Understand different classes of drugs, their mechanism of action, dynamics, kinetics, structure activity relationships, pathophysiology and pharmacotherapeutics of various diseases.

PO13 **Drug development:** Ability to synthesize, develop and/or evaluate various pharmaceuticals and their formulations and cosmeceuticals products

PO14 **Analytical skills:** Develop skills in qualitative and quantitative analysis of various pharmaceuticals.

PO15 **Training:** Acquire technical knowledge and hands on training on equipments, instruments and software used in the field of pharmaceutical sciences.

**- PO12-15 are program specific outcomes*

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तमसो मा ज्योतिर्गमय

EDITORIAL MESSAGE

The demographics reports that nearly 17% of the world's population will be aged 60 years and above by 2030. The aging population is becoming progressively cognizant and concerned about the onset of degenerative diseases such as Parkinson's and Alzheimer's. Individuals using supplements such as vitamins, minerals, protein, and omega-3 to slow down or check the onset of degenerative diseases are rising. Global Wellness Supplement markets are witnessing robust growth and plans for market expansion into developing countries. The global vitamins market size will grow by over USD 24.1 billion during 2019-2023. The year 2019 is expected to remain strong for the wellness Supplement market growth due to expanding applications and increasing consumer role. Also there is rising competition which act as challenges for the market growth to 2025.

In this issue we have invited articles from food and nutrition experts as well as the regulatory experts together with postgraduate and undergraduate students spread across different facets of pharmaceutical field.

We are thankful to all the faculty members, our Director as well as our Director General Dr. Anup Singh and the Nirma University authorities, stakeholders, reviewers for all the support provided in rolling out this issue. We hope that our efforts will help the readers to widen the horizons.

We look forward to your constructive criticism and suggestions.

Happy hours!!

Editorial Team, NUJPS

editor.nujps@nirmauni.ac.in

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REVIEW ARTICLE

NUTRITIONAL STATUS ASSESSMENT OF PRESCHOOL CHILDREN ATTENDING ANGANWADI CENTERS OF AHMEDABAD CITY

Renu Singh, Jagruti Chauhan, Alka Sanghvi, Nayan Jain
Food Science and Nutrition, Gujarat University, Ahmedabad

Abstract:

Preschool children age group is a vulnerable population which seeks more attention and care on nutritional status. For the present study 142 children aged two year to five year were purposively selected. The data were collected by pre-prepared questionnaires. Anthropometric measurement was done by weight, height, Middle Upper Arm Circumference (MUAC), Head and chest circumference, BMI. Severity of malnutrition was assessed by Weight for age, height for age and weight for height. The study revealed 36.6 percent children were stunting and 16.9 percent were severe stunting, 23.9 percent children were underweight while 30.3 percent children were severely underweight, 5.6 percent children were fall under severe wasting category while 19 percent children were fall under wasting category. The results of the study indicates that under nutrition is still an important public health problem among children in Isanpur area of Ahmedabad and was significantly associated with gender, family income, education of mother, as well as dietary intake. Personal hygiene and sanitation, dietary intake might help to improve nutritional status of children

Keyword: Anthropometric measurements, chest circumference, malnutrition, wasting, dietary intake

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1. INTRODUCTION

Malnutrition among under – five year children is an important concern for the health authorities in India. Child malnutrition is very important factor and it is significantly associated with the risk of infant and child death, with some estimates suggesting that child malnutrition is responsible for half or more of child deaths in the developing world[1,2]. Nutritional status of children belong to age group under five year is one of the important indicator of overall development of community and thus country. Children living in rural and tribal areas of India are at high risk of under nutrition because of incorrect nutrition, sanitation coupled with low hygienic practices and other condition.

At present in India 48% children under 5 years age are chronically malnourished and 43% are underweight[3]. More than half (54%) of all deaths before age five years in India are related to malnutrition. Because of its extensive prevalence in India, mild to moderate malnutrition contributes to more deaths (43%) than severe malnutrition (11%)[4]. Growth assessment best defines the health and nutritional status of children because disturbances in health and nutrition regardless of their etiology invariably affect child growth and hence provide an indirect measurement of the quality of life of an entire population. The study of National Nutrition Monitoring Bureau also reported high prevalence of underweight (53%) among < 5 years children in the rural areas of Gujarat during 2011-12[5]. Maternal factors like age, education and their nutritional status also play a significant role in child's nutritional status, thus it is very important to encourage social status of women for the uplifting of the child nutritional status. [6, 7, 8]

India would be raising a generation which is debilitated and unable to contribute effectively to the productivity of the country .The Government has accorded high priority to the issue of malnutrition in the country and is implementing several schemes/programmes under different Ministries/Departments through State Governments/UT Administrations. Ministry of women and child development government of India took initiation to combat malnutrition among children through ICDS programme. The Integrated Child Development Services Programme aims at providing services to pre-school children in an integrated manner so as to ensure proper growth and development of children in rural, tribal and slum areas and it has been found that majority of the children has good nutritional status who received nutrition trough ICDS programme.[9,10]

OBJECTIVE

1. To assess the health and nutritional status of ICDS beneficiaries, especially 2 - 5 years age –group children in the urban area of Ahmadabad district, Gujarat.

2. To assess the malnutrition in terms of underweight, wasting, and stunting in children aged 2 years - 5 years (60 months) of age registered in Anganwadi Centres in urban area of Ahmedabad.

MATERIALS AND METHODS

The present study was carried over a period of four months with the aim to obtain information about "Nutritional status with special reference to malnutrition in preschool children attending Anganwadi of south Ahmedabad District, Gujarat".

A group of 142 subjects of 2 - 5 year of age attending Anganwadi centers in urban area of south Ahmedabad city in Gujarat were selected through purposive sampling technique. The study was approved by the Institutional ethical committee and informed Consent was taken from respected authorities as well as from parents or caretakers of children. Demographic information were collected; specific information like infant and young child feeding practices, history of morbidity, Interest of children in going at Anganwadi and like or dislike the taste of food or food products provided by Anganwadi was also collected by children's guardians. Dietary survey of the sample was conducted by using 24 hours dietary recall method for 3 days using standardized cup sets and by food frequency method to assess their food and nutrient intake. [11]

Anthropometric measurement was done by weight, height, MUAC, Head and chest circumference, BMI. Severity of malnutrition was assessed by Weight for age, height for age and weight for height according to WHO growth standards [12]. Clinical signs were also observe and diet recall and food frequency method was taken to assess the dietary intake of children's.

RESULTS AND DISCUSSION

The total number of registered children (2-5 years) in the surveyed Anganwadi Centers was 142. The growth monitoring at Anganwadi Centers was done only up to 5 years of age. Thus, the actual study population comprised of 142 children of 2-5 years age group.

TABLE: 1- Frequency Table with MUAC Distribution

LEVEL	MODERATE (11.5 TO 12.4 CM)		AT RISK (12.5 TO 13.4 CM)		NORMAL (>13.5 CM)	
	No.	Percentage	No.	Percentage	No.	Percentage
GIRLS	0	0	9	11.4	70	88.6
BOYS	1	1.6	9	14.3	53	84.1
TOTAL	1	0.7	18	12.7	123	86.6

Table 1 showed that out of 142 children, 123 children (70 girls and 53 boys) were fall under normal grade (86.6 %), 18 children (9 girls and 9 boys) were at risk (12.7 percent) and 1 boy and no girl were fall under moderate grade (0.7%).

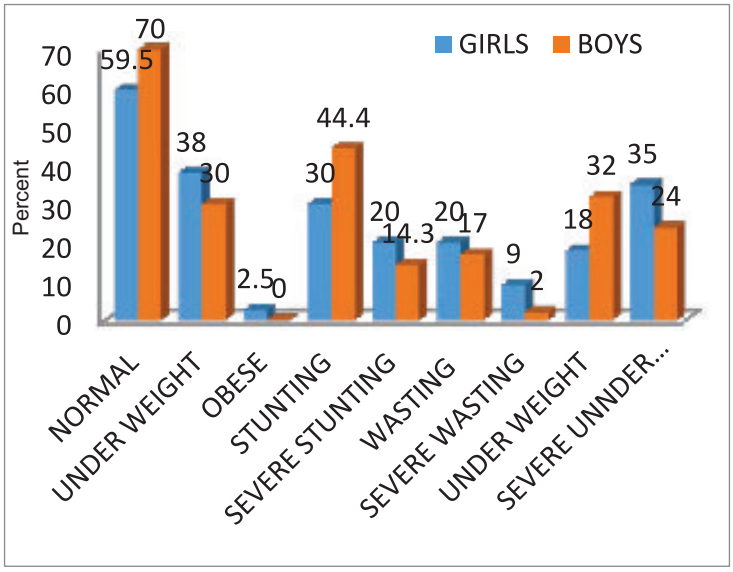

FIGURE: 1 Nutritional Status of Children of According to Height for Age

Figure 1 showed that malnutrition was quite prevalent in the children both towards overweight and underweight. The table showed that the nutritional status of children according to height for age showed that 30 percent girls and 44.4 percent boys were stunting. 20 percent girls and 14.3 percent boys were severe stunting, while weight for age showed that 18 percent girls and 32 percent boys were under weight. 35 percent girls and 24 percent boys were severe underweight, weight for age showed 20 percent girls and 17 percent boys were fall under wasting category and 9 percent girls and 2 percent boys were fall under severe wasting category. None of the infants exhibited the clinical signs of nutritional deficiency.

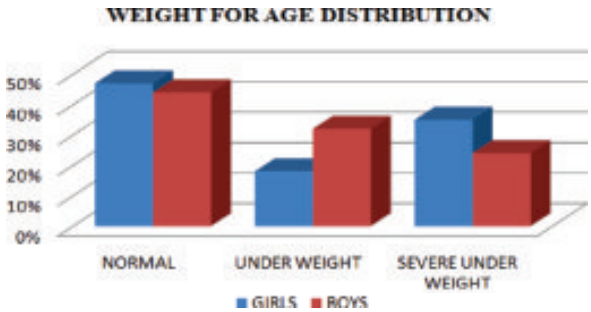

FIGURE: 2 - Nutritional Status of Children of According to Weight for Age

Figure 2 showed the nutritional status of children according to weight for age. It showed 47 percent girls and 44 percent boys were normal, 18 percent girls and 32 percent boys were under weight, 35 percent girls and 24 percent boys were severe underweight.

TABLE: 2 -Nutritional Status of Children of According to Weight for Height.

GENDER	NO.	NUTRITIONAL STATUS							
		NORMAL		WASTING		SEVEAR WASTING		RISK OF OVER WEIGHT	
		NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
GIRLS	79	55	70	16	20	7	9	1	1
BOYS	63	51	81	11	17	1	2	0	0
TOTAL	142	106	74.7	27	19	8	5.6	1	0.7

Table 2 showed the nutritional status of children according to weight for height. It showed 70 percent girls and 81 percent boys were normal. 20 percent girls and 17 percent boys were wasting. 9 percent girls and 2 percent boys were severe wasting. Only one of girl was at risk of overweight, while none of the boys were fall in this category.

TABLE: 3 - BMI distribution among girls and boys

	NORMAL	UNDER NOURISHED	OBESE
Girls Frequency	47	30	2
Percentage	59.5	38	2.5
Boy Frequency	44	19	0
Percentage	70	30	0

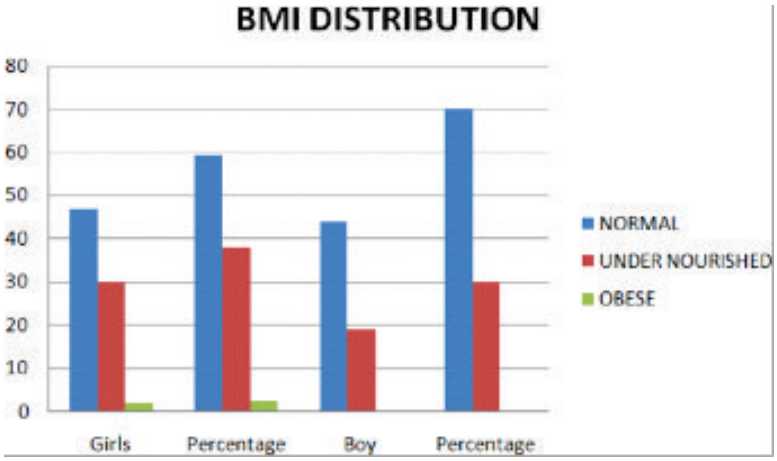

Figure: 3 - BMI Distribution of Boys and Girls

Figure 3 and Table 3 showed the BMI distribution of girls and boys. The graph showed that 59.5 % girls and 70 % boys were have normal BMI, 2.5 % girls were overweight while none of the respondents were obese in boys figure 3 also showed that38 % girls and 30 % boys were undernourished .

TABLE: 4 - Nutrient Intake of 4-5 Years Children

NUTRIENTS	RDA	GIRLS MEAN +	(%) of RDA	BOYS	(%) of RDA
ENERGY	1350 kcal	753.62 + 50.42	55.82	775.33 + 31.14	57.43
PROTEIN	20.1 gm	16 + 1.07	80	18 + 0.65	89.5
FAT	25 gm	21.54 + 2.08	86.16	21.60 + 1.15	86.4

The information pertaining to the food consumption pattern of the children was collected by 24 hour recall method and food frequency method. While comparing the nutrient intake with RDA it was seen that subjects of 4-5 years consumed all the nutrients in lesser amounts. Table 4 showed that total energy intake of girls was 55.8 percent; protein was 80 percent and fat was 86.16 percent. 57.4. Total energy intake of boys was 57.43 percent, protein 89.5 percent, fat 86.4 percent.

TABLE: 5 - Food Frequency of children

FOOD ITEMS	Never Or Rarely	Once A Week	Several Times A week	Once A Day	Two or More Times A Day
Dairy Products	14%				86%
Meat Products Meat, Fish etc. Egg	 77% 74%	 23% 26%			
Pulses & legumes				100%	
Cereals & cereals products				100%	
Fruit Products	20%	10%	70%		
Vegetable Products: Roots and tubules Green leafy vegetables	25%		 100% 75%		
Sweets					100%
Fats (butter, oil, ghee)					100%

Table 5 showed that 14 percent of children never consumed milk and other dairy products, whereas 86 percent children consumed milk and other dairy products, two or more times in a day. 77 percent children never consumed meat or meat products while 23 percent children consumed meat or meat products once in week. 74 percent children never consumed egg and 26 percent children consumed egg once in week. 100 percent children consumed Pulses and Legumes, Cereals and Cereals products on daily basis. 20 percent children never consumed fruits while 10 percent children consumed once in week and 70 percent consumed several times in week.100 percent children consumed roots and tubules several times in week. 25 percent children rarely consumed green leafy vegetables while 75 percent consumed several times in week. 100 percent children consumed sweets two or more times in day.100 percent children consumed fats two or more time. Overall study revealed that intake of cereals and legumes in moderate amount, intake of milk and dairy production in less amount, meat and egg consumed once in a week, consumption of green leafy vegetables were rare or less, fruits consumption is also less.

TABLE: 6 - Hygiene status of Children

Sr. No.	Questionnaire	Number and Percentage			
		DO		DON'T	
1.	Do you wash your hands? a. before eating /after eating b. after using toilet c. after playing	Number	(%)	Number	(%)
		138 142 121	97 100 85	4 0 21	3 0 15
2.	Do you take bath daily?	137	96.5	5	3.5
3.	Do you brush daily?	98	69	44	31
4.	Does the child have clean hair?	126	89	16	11
5.	Has the child cut his/her nails?	112	79	30	21

Detail of Hygiene status of children is given in Table 6. About 97 percent of children were washing their hand before / after eating while 3 percent children were not. 100 percent of children are washing their hands after using toilet and there are 85 percent children wash their hands after playing while 15 percent children were not. About 96.5 percent children take daily bath while 3.5 percent children are not taking bath daily. There are 69 percent children do brush daily while 31 percent children do not take daily brush. There are 89 percent children have clean hair, 11 percent children have unclean hair. 79 percent children have cut their nails while 21 percent children haven't cut their nails.

CONCLUSION

The above results showed the overall children's nutrient intake was poor, their energy intake was low when compared to RDA it was found that their fat and protein intake was also less. Most of them were belong to lower income group so it may be one of the reasons of improper intake of food and malnutrition. Mothers were less educated so it also relates to poor nutrition intake of their child because of knowledge of nutrient and there RDA was not known. Nutritional level of boys was better than girls.

The results of the study indicates that under nutrition was still an important public health problem among children in Isanpur area of Ahamedabad and was significantly associated with gender, family income, education of mother, as well as dietary intake. Personal hygiene and sanitation, dietary intake might help to improve nutritional status of children.

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REVIEW ARTICLE

REGULATORY DOSSIER SUBMISSION AND REVIEW PROCESS IN EUROPE

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Abstract:

This article discuses the process of marketing authorization application and its regulated evaluation at agency's end in the region of Europe. The cluster of 28 European Union (EU) member states, 3 European Economic Area (EEA) and European Free Trade Association (EFTA) states make European Union. As European nation consists of larger population, the government is alert regarding safety of the public health in EU. In the Europe, authorization of product is mandatory before they can be placed on the market in order to protect public health and ensure the availability of high quality, effective and safe medicines for European citizens. European drug authorization system offers different routes for such marketing authorization and same is discussed in this article.

Keyword: MA, EU, Data protection, Centralized Procedure, Mutual Recognition Procedure, Decentralized Procedure, National Authorization

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INTRODUCTION [1, 2]:

The European regulation major objective is to protect public health and at the same time encourage the development of the pharmaceutical industry of the EU. Marketing authorization (MA) (i.e. product license) must be obtained before marketing a medicinal product in the EU. The company (it is more specifically called as "Marketing Authorization Holder" in Europe) which is responsible for placing the medicinal product on the market should be established within the European Economic Area (i.e., Iceland, Liechtenstein, Norway and the Member States of the EU). European regulation has established as well as harmonized many aspects of regulating the production, distribution and safe use of medicines in the EU.

A foremost and significant measure was done in the year 1995 by creating the European Medicines Agency (EMA) and the establishment of a Centralized procedure, through which a single EU wide evaluation was done for granting of approval of new medicines.

Drug approval process in Europe:

The drug approval process is termed as a regulatory process to get authorization to launch the medicinal product in the market for sale. This activity involves different phases : giving application in order to review for conduct clinical trials, then conducting clinical trials and further application to marketing authorization of drug and post-marketing studies. The applicant files a regulatory dossier to apply for marketing authorization (MA) to agency for evaluation. The filing is done by applying suitable regulatory procedure considering the product type. Each nation has its own regulatory drug authority, which is responsible for enforcing rules, regulations and guidelines which are to be followed by applicant. Through this way regulation for marketing of the drugs is controlled. Regulation procedure of agency is shown in Fig 1.

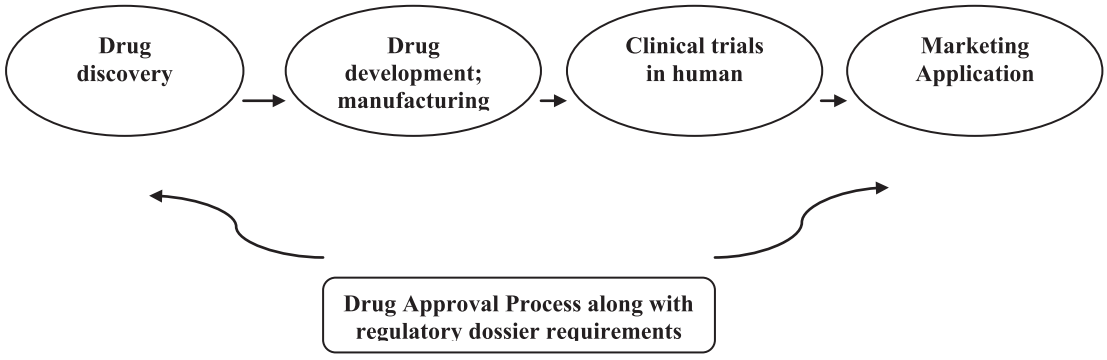

Figure 1 : Regulation procedure

Marketing Authorization Application [2]:

Marketing authorization (MA) is defined as the procedure of review and evaluating the dossier to support a medicinal product in view of its requirements for marketing (i.e. registration, license approval) and then issuing a finalized document. The application dossier for marketing authorization is declared as a Marketing Authorization Application (MAA) in the European Union.

Concerned competent regulatory agency monitors Quality, Safety and Efficacy for MA grant.

Only after a marketing authorization (MA) has been issued, medicinal product in the European Union is placed on the market. It can be granted through:

a) the competent authority of a Member State (National authorizations) or

b) the Commission for the whole EU (Union authorization).

DATA EXCLUSIVITY/MARKET PROTECTION/GENERICS [3, 4]:

The originators of new drugs have invested a lot of various resources for inventing the new drug. Hence, the regulations are framed in such a way that entry of generic copies of new drug is restricted onto the market for a set time periods. This is done to encourage and reward the innovators.

Data Exclusivity:

It is the duration of time during which an applicant cannot depend on the data in support of another marketing authorization for the purpose of submitting an application, obtaining marketing authorization or placing the product on the market. Health agencies cannot start validation of generics, hybrids or biosimilars during this phase.

Market Protection:

It is the duration of time during which medicinal product cannot be placed on the market even though it has already received a marketing authorization. The medicinal product can be a generic, hybrid or biosimilars.

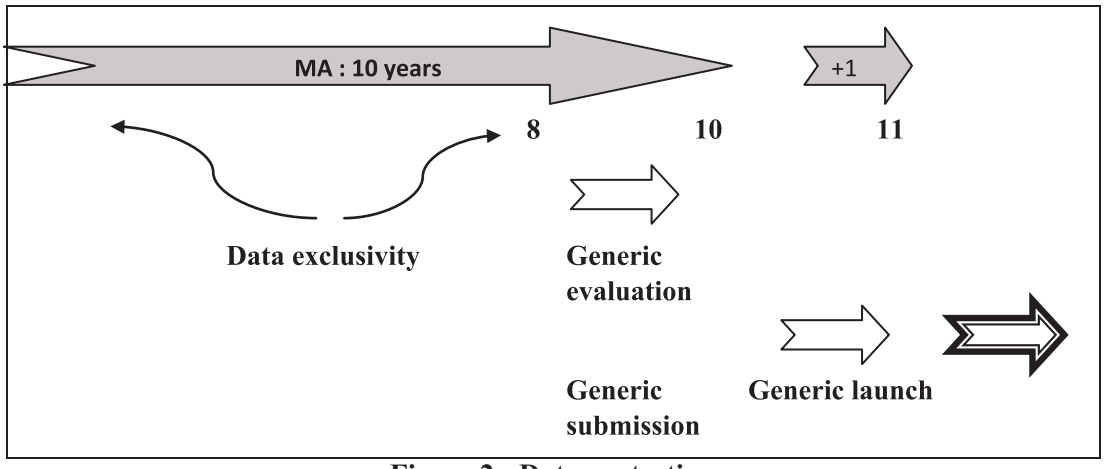

Figure 2 : Data protection

Once an authorized new drug patent expiry happens, manufacturers will wish to introduce generic copies of it in the market to sell their products. However, pre-clinical and clinical data are not submitted, if the bioequivalence with the approved reference drug is demonstrated by the applicant (generic)

The authorization of generic medicinal products is covered by Article 10 of the Human Medicines Directive 2001/83/EC and Article 13 of the Veterinary Medicines Directive 2001/82/EC.

A generic drug is defined as a medicinal product that has:

- the same qualitative and quantitative composition in active substances as the reference product;
- the same pharmaceutical form as the reference medicinal product;
- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Regulatory submission dossier modules [5]:

The applicant has to submit regulatory dossier in preferred format for new marketing authorization. All regulatory documents have to be submitted in compliance to the CTD format. The complete guidance on documents requirements for dossier application is presented in volume 2B, NTA, July 2003 edition. Additional guidance is updated on website of European agencies regularly. Five CTD modules are structurally presented in the marketing authorization application. Below is the brief tabulated list of dossier module contents:

Table : 1 - Dossier module contents

Module	Contents	Details
1	EU administrative and prescribing information	Application form Summary of Product characteristics Labelling texts and mock ups Information about the experts Environmental risk assessment Orphan market exclusivity Pharmacovigilance system Risk management plan
2	Summary	Quality Non-clinical overview Non-clinical summary Clinical overview Clinical summary
3	Quality	Body of data References
4	Non-clinical	Study report References
5	Clinical	Study report References

Procedures for marketing authorization of medicinal products in Europe:

The marketing authorization application can be made through four ways as below:

1. Centralized Procedure
2. Mutual Recognition Procedure
3. Decentralized Procedure
4. National Procedure

European Union (EU) [1]:

The EU regulatory systems is one of the most highly regarded reputed systems in the world. The system consists of European parliament, the council of ministers and the European Commission. European Union consists of 28 member states: Austria, Bulgaria, Belgium, Cyprus, Croatia, Czech Republic, Denmark, Estonia, France, Finland, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Latvia, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Slovenia, Sweden, and the United Kingdom and three countries which are member of European Free Trade Agreement (EFTA) Norway, Iceland and Liechtenstein. These EFTA members are those countries which were not part of the 28 member states as common market. These three EFTA member countries along with 28 EU member states, comprises of the European Economic Area (EEA).

The European Medicines Agency (EMA) is a decentralized agency of the European Union, located in London. The responsibility of Agency is the scientific evaluation and assessment of medicines developed by pharmaceutical companies for use in the European Union(EU) and applications for European marketing authorizations for both human and veterinary medicines (centralized procedure). Under the centralized procedure, single marketing-authorization application to the Agency is submitted by the applicant. Once marketing authorization is granted by the European Commission, a centralized (or "Community") marketing authorization is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway).

This network is what makes the EU regulatory system unique.

Centralized Procedure (CP) [6, 7, 8]:

As per the regulation (EC) No 726/2004, Centralized procedure is described for marketing application of medicinal products, for which only single application, single evaluation and single authorization is required for marketing medicinal product into entire community market. By this procedure medicinal product can be available into all member states of European Union. The scope of medicinal product for which application is to be made is divided into three parts:

a) Mandatory
b) Optional
c) Generic/Hybrid

a) Mandatory scope:

Medicinal products as per below category fall into the mandatory scope according to EU regulation 726/2004:

- Medicinal products developed by recombinant technology, expression of proteins in prokaryotes and eukaryotes cells & hybridoma and monoclonal antibody methods.
- Medicinal products with a new active substance for the treatment of AIDS, cancer, neurodegenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions and viral diseases.
- Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

b) Optional scope:

Medicinal products containing other new active substances may, at the request of the applicant, be considered for evaluation under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, technical or scientific innovation, or the granting of a Community authorization is in the best interests of patients at the Community level.

c) Generic/Hybrid:

A generic/hybrid product of a reference medicinal product authorized via the CP has automatic access to the centralized assessment under this scope.

In current scenario, a good number of majorities of new innovative medicines get ahead through the centralized authorization procedure in order to be marketed in the EU.

The schematic procedural timetable for evolution of application is done by EMA is as follows:

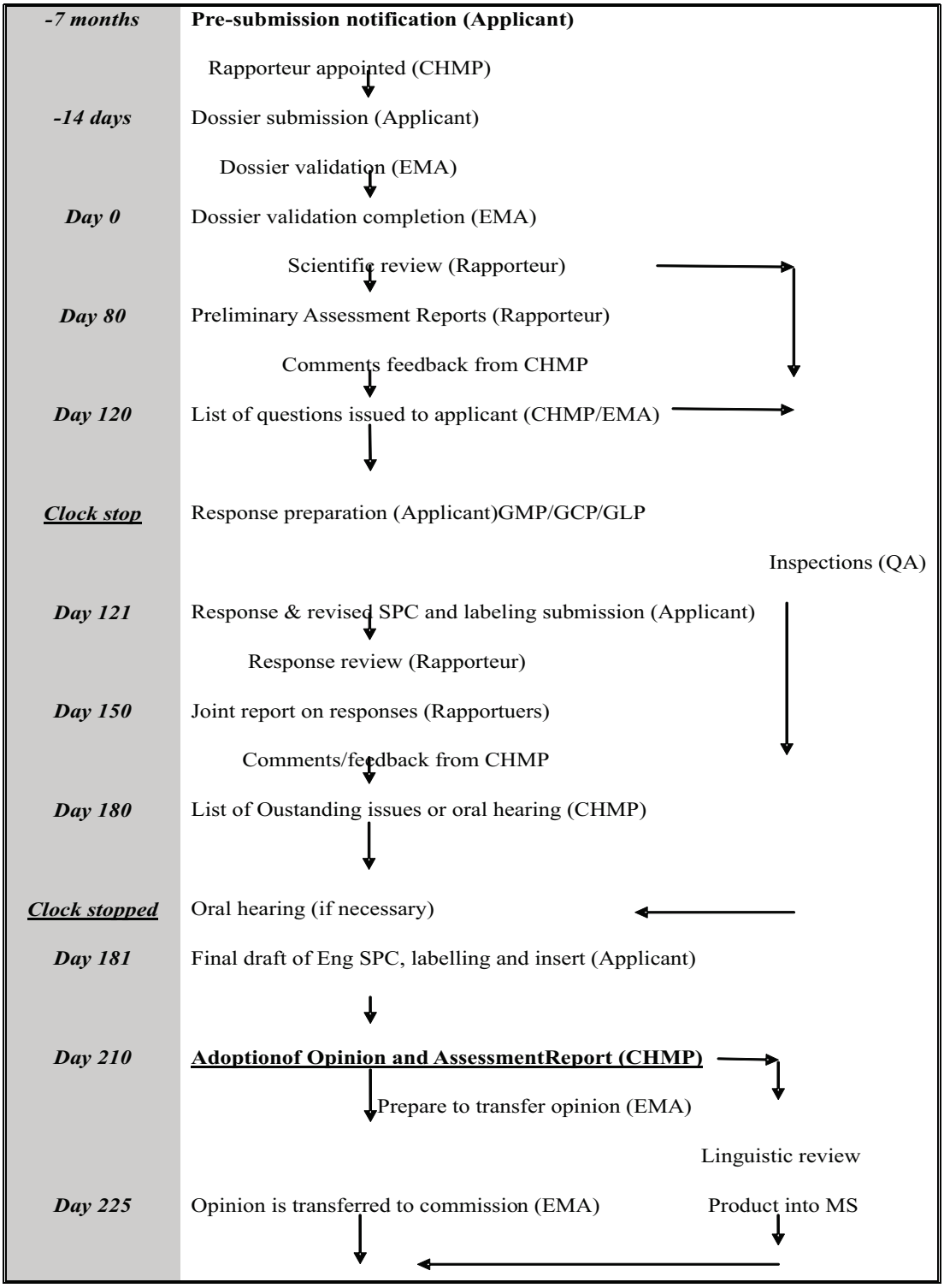

Figure: 3 - Schematic procedural timetable by EMA

Accelerated assessment [7-10]:

The EU has introduced the accelerated assessment and evaluation in November 2005.The aim for this accelerated assessment is to pace up the regulatory procedure in order to facilitate patients access to new medicines. The request for accelerated assessment and evaluation should be made at least two to three months prior to submitting the marketing-authorization application.

The centralized procedure marketing-authorization application's evaluation can take up to 210 days excluding the procedural clock stops when applicants have to provide additional information. On request, the CHMP can reduce the timeline to 150 days provided if the applicant submits sufficient justification for an accelerated assessment of the MA application.

Article 14 (9) of Regulation (EC) No 726/2004, states that "when an application is submitted for a marketing authorization in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure".

Approval of CPMA [9-12]:

Assessment of the application by the CHMP is published initially as a summary of Opinion, whether positive or negative.

After the granting of a MA by the EC a more detailed report is published as the EPAR on EMA website.

The EPAR shows the scientific conclusion reached by CHMP at the end of the centralized evaluation process. It is accessible to the public, in which the commercial confidential information is removed. The EPAR gives a summary of the reasons of the CHMP opinion in favour of granting a MA for a specific medicinal product.

EPAR is presented as a sequence of documents and includes: a lay summary, product information (SmPC/PL/label), details about the marketing authorization holder, and discussion about the evaluation carried out at EMA. It comprises based on the review of Committee on the documentation furnished by the applicant & from succeeding discussions held during CHMP meetings. The EPAR is updated throughout the authorization period (life cycle of product) as changes to the original terms and conditions if the authorization (i.e. pharmacovigilance issues, variation, specific obligations) is made. The EPAR also contains a review written in a manner that is understandable to the public.

Mutual Recognition Procedure [8, 13-14]:

A medicinal product is first authorized by one member state, as per the regulations of its own national procedure. The applicant can seek further authorizations based on that existing MA through a mutual recognition procedure.

The MRP is stated in Council Directive 93/39/EEC. That is, once a drug is approved for marketing authorization (MA) by one member state, the pharmaceutical company can apply for MA in other member states through the MRP.

After getting the first authorization it is easy and quick to get for further member states because medicinal product already exists in European market and it helps to prove that product is therapeutically effective.

The applicant submits identical applications to those member states where marketing authorizations are required.

The member state that reviews the application first is called the 'Reference Member State'.

It notifies other states, called CMS .i.e. Concerned Member State. CMS may delay their own evaluations to await assessment by the RMS.

The Reference Member State (RMS) shall prepare or update the assessment report within 90 days of receipt of a valid application. The assessment report together with the approved summary of product characteristics, labeling and package leaflet shall be sent to the Concerned Member States and to the applicant by RMS.

The decision of the RMS is forwarded to the CMS.

If the CMS reject mutual recognition, the subject is referred to the Committee for Medicinal Products for Human Products (CHMP) of EMA for arbitration. EMA forwards its opinion to the EC, which makes the final decision.

Table : 2 - Schematic presentation of mutual recognition procedure

90 days prior to CMS	Applicant requests RMS for AR and procedure number allocation.
Day -14	Applicant submits the dossier to CMS. RMS do circulation of the AR including SmPC/PL/Label to CMSs. Validation of the application is done by CMSs.
Day 0	RMS starts the procedure.
Day 30	CMSs send their comments to the RMS, CMSs and applicant.
Day 40	Applicant sends the response document to CMSs and RMS.
Day 48	RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 55	CMSs send their remaining comments to RMS, CMS and applicant.
Day 55-59	RMS & Applicant in communication to close the procedure or to submit response.
Day 60	RMS closes procedure if no CMS comments at Day 55.
Day 60-90	Used only if CMS had Day 55 comments.
Day 68	RMS evaluates response and circulate AR.
Day 75	CMS send remaining comments if any.
Day 85	Final CMS position.
Day 90	CMSs give notification to RMS and applicant of final position. "If consensus is reached, then RMS closes the procedure. and if not reached then the points for disapproval submitted by CMS(s) are referred to Co -ordination group for Mutual Recogn ition and Decentralised Procedures – Human (CMD(h)) by the RMS within 7days".
Day 150	For procedures referred to CMD(h): If consensus is reached at the level of CMD(h), procedure closed and If not reached then, RMS refers the matter to CHMP for arbitration.
5 days after	High quality national translations of SmPC/PL/Label are sent to CMSs by applicant.

Decentralized procedure [8, 13, 15]:

Directive2004/27/EC regulates Decentralized procedure that came into effect in the European Union in 2005 .The primary aim of this procedure is to obtain marketing authorizations in several Member States, even though there is no existing marketing authorization in the European area. For medicinal products not falls within the mandatory scope of the centralized procedure, the applicant may request one or more concerned Member State(s) to approve a draft assessment report, labeling, summary of product characteristics (SmPC), and package leaflet as proposed by the chosen reference member state. An application is submitted to the competent authorities of the Reference Member State and the concerned member state(s), together with the data and particulars referred to in Articles 8, 10, 10a, 10b, 10c, and 11 of Directive 2001/83/EC.

Steps involved in Decentralized Procedure:

The applicant submits an application to the respective health agencies of each member states, where the applicant wants to acquire a marketing authorization. In contrast to MRP, in DCP the applicant may assign a country to act as the Reference Member State. DCP slot booking procedure is done by applicant. The RMS selection procedure is depended on various criteria like previous experience, workload, interests of the applicant and acceptance of the applied dossier by the RMS.

The RMS will start to assess dossier application once both the RMS and all the CMS(s) agree on validity of procedure. The RMS then prepares and forward a preliminary Assessment Report on the submitted dossier to the CMS(s)and the applicant in a period of 70 days based on assessment. The CMS(s) gives their comments. The RMS will forward all observation and remarks received from the CMS(s) to the applicant on day 105 and stop the clock if required, till the time that the applicant prepares a response document for the comments sent. The RMS prepares a Draft Assessment Report on day 120 and if a consensus has been reached between the CMS(s) and the RMS; the procedure may get closed. Otherwise the CMS(s) has 90 more days to approve the Draft Assessment Report and other documents.

RMS and CMS(s) authorities agree to a decision within 30 days after acknowledgement of their agreement to the Assessment Report and other documents during the national phase. A national marketing authorization will be issued in the RMS and each of the CMS(s) after the positive agreement.

For DCP, it is very much required that competent authorities ensure that assessment reports are released on time in accordance with the DCP timetable. This will be possible by good communication between the applicant and the Reference Member State (RMS).

Competent authorities should do their best endeavor to avoid delay in the start of the procedure.

Table : 3 - Schematic presentation of decentralized procedure

14 days prior	Applicant discusses with RMS. RMS allocate procedure number.
Day -14	Dossier submission to RMS/CMSs
Assessment Step I	
Day 0	RMS starts the procedure.
Day 70	RMS forwards PrAR + comments on SmPC/PL/Label to CMSs & Applicant.
Day 100	CMSs send comments to RMS, CMSs & Applicant.
	RMS may consult CMS to close procedure.
Day 105	RMS closes the procedure or stops the clock.
	To allow applicant to respond the comments and s upplementation of dossier.
Clock off period	Applicant submit the draft responses to RMS/CMSs. Final responses are sent within a recommended period of 3 months, which could be extended further 3 months if justified.
Assessment Step II	
Day 120 (Day 0)	RMS sends draft AR/SmPC/PL/Label to CMSs + Applicant.
Day 145 (Day 25)	CMS sends comment to RMS/CMSs/Applicant.
Day 150 (Day 30)	RMS may close procedure if consensus reached.
	Proceed for 30 days National MA Grant.
Day 160	Applicant submits response to RMS/CMSs.
Day 180 (Day 60)	If consensus reached then RMS closes the procedure.
	If not reached then; RMS prepares AR on outstanding issues.
Day 195	A break out session. CMSs send final comments.
Day 195-210	RMS consults with the CMSs / Applicant to discuss t he remaining comments raised.
Day 210 (Day 90)	**Closure of the procedure**. Proceed for 30 days National MA Grant.
	or
	If consensus not reached then referral to the Coordination Group.
Day 270	Final position adopted by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement.
National Step	Applicant sends high quality national translations for SmPC/PL/Label.
7 day after EOP	

DCP is a modernized procedure with the possibility for shorter approval times in simple cases. The DCP is a single procedure that could end at different stages taking into account:

- Harmonization of originator SmPCs;
- The quality of the file;
- The assessment report;

It is possible to end the procedure at any time point during the procedure if agreement is reached.

National Authorization Procedure [8, 16]:

Apart from the products that fall within the scope of Community Authorizations, all other products can only be licensed via application to the Competent Authorities of individual Member States. However, through the use of either decentralized or mutual recognition procedures it is possible to obtain authorizations on the basis of a dossier assessment conducted by a single Member State.

If the applicant want to get the marketing authorization in only one member state then marketing authorization application should be made to national competent authority of respective member state. In such application while taking the national marketing approval, the medicinal product should not be approved in other member state of European area under same sponsor.

Since the approval for the marketing of product is granted directly by the respective member state authority; sponsor will get faster approval compared to other procedures.

The competent authority is responsible for reviewing and granting MA. This procedure is applied for new active substances which are not mandatory under Centralized procedure. Most of the regulatory agency requires 210 days for review and approval of MAA; however it may vary slightly from agency to agency of different member states followed by national phase for translation activities.

In current scenario, national procedure application is made very limited in number. In situation when a slot to run DCP with the RMS is not available or in cases when RMS does not want to access the complex molecule as a part of DCP, national procedure is applied. Usually in such instance, the applicant gets approval of medicinal product nationally and then further extends the MA in other member states via Mutual Recognition Procedure.

Well-established Medical Use products [4]:

The EU will accept marketing authorization applications without supporting pre-clinical and clinical studies, if it can be demonstrated that the active substances have been in well-established use in the Community for at least 10 years, with sufficient efficacy and an acceptable level of safety. This route of application can be appropriate for many common over-the-counter (OTC) products. Safety and efficacy is supported by providing copies

of published scientific literature as part of the submission; that is, the submission relies on safety and efficacy data available in the public domain, as opposed to confidential data from authorized applications that is the cornerstone of generic applications.

Renewal [17-18]:

After marketing authorization expiry if applicant wants to continue the sale of the medicinal product into the market; then renewal of the marketing authorization is a must act. For the renewal of the marketing authorization, applicant must apply before nine months of the expiry of medicinal product in market. In this regard, it is noted that the renewal should take place upon the expiry of the period of five years and that decision of granting renewal is based on the consolidated file submitted by MAH for this purpose, that the benefit-risk is positive.

A premature submission for renewal may not be sufficiently up to date for the Commission/Competent Authorities to adopt a decision on the renewal.

If there is agreement at the end of the procedure that the benefit/risk of the product remains favorable and there are no pharmacovigilance issues that would require a further renewal, the MA may be granted unlimited validity.

Sometimes it happens that there are changes in the product information, the renewal documents issued will include the SmPC and harmonized leaflet and label texts.

On the basis of the overall re-evaluation of the risk-benefit balance, the CHMP may recommend to grant unlimited validity to the Marketing Authorization, or to require one additional five-year renewal. The grounds on which the CHMP may decide to require an additional renewal will be duly justified and mostly it is related to pharmacovigilance. For example, exposure of an insufficient number of patients to the medicinal product.

Conclusion:

The legislations, directives and guidelines as laid by European Commission and CMD (h) are to safeguard public health, safety and patients' well-being. The health agency of various member states follows strict vigilant evaluation of the regulation dossier submitted by the applicant to obtain a marketing authorization. The MAA in Europe can be obtained through any of the regulatory procedure (CP, DCP, MRP and NP) on the basis of application scope. Renewal procedure is filed before nine months of MA expiry if the applicant wants to continue the sale of medicinal product.

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Abbreviation:

CTD: Common Technical Document

CHMP: Committee for Medicinal Products for Human Use

CMD (h):Co-ordination group for Mutual recognition and Decentralized procedures – human

EU: European Union

EEA: European Economic Area

EFTA: European Free Trade Association

EOP: End of Procedure

EMA: European Medicines Agency

EPAR: European Public Assessment Report

PrAR: Preliminary Assessment Report

PL: Patient Leaflet

SmPC: Summary of Product Characteristics

MA: Marketing Authorization

MAH: Marketing Authorization Holder

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REVIEW ARTICLE

BIORELEVANT DISSOLUTION MEDIA: ITS CURRENT STATUS AND FUTUTRE PERSPECTIVES

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Abstract:

The landscape of dissolution media has been dynamically evolving with newer drugs entering the market among which most of them are either BCS class II or BCS class IV drugs exhibiting poor solubility. Conventional dissolution raises lot of doubts in the pharmaceutical industry owing to its composition which fails to adequately mimic in-vivo conditions. The effect of bile salts, enzymes are prevalent factors which are often neglected by conventional dissolution media. To overcome these hurdles biorelevant media was suggested by several research groups and several developments have been witnessed to maintain a proximity to the required in-vivo conditions during dissolution. Media such as simulated gastric fluid, simulated intestinal fluid, milk-based dissolution media (Ensure®) have been suggested for fast and fed state taking into the considerations several factors like pH, surfactant concentration, etc. The recent improvement has been on fast state simulated intestinal fluid (FaSSIF- V2) where replacement of acetic acid by maleic acid is evident. Though biorelevant dissolution media has solved the primary hurdle of mimicking in-vivo conditions, it has still not been accepted as a quality control tool to test batch to batch consistency in pharmaceutical industry. The reasons being cost, time consumption and basic requirement of dissolution as test as discriminatory tool where biorelevant media fails at certain fronts where conventional dissolution passes fairly well. The use of surfactants like bile salts in biorelevant media shows increased dissolution profile of different batches and fails to discriminate between them. It is a common understanding that those compounds

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which show increased dissolution in conventional media are obvious to show better dissolution in biorelevant media. This is the reason why conventional media are preferred over biorelevant media during quality control evaluation and batch to batch variability tests to save cost and time. Biorelevant media are being used today majorly during developmental stages and still need to go a long way to be used as quality control tool.

Introduction:

The concept of dissolution was sown more than century ago in 1897 when Noyes & Whitney studied the dissolution of two sparingly soluble compounds, benzoic acid and lead chloride. The experimental set up was conceptually similar to the modern-day dissolution set up having a cylinder immersed in water held at constant temperature and contents inside rotated at constant speed [1]. The work led to the establishment of basic dissolution equation which is Noyes-Whitney equation. By 1950s the value of dissolution and it's testing in rate of absorption of dosage form was well understood. Today dissolution is not only used for drug development and quality control to check lot-to-lot consistency but also to check the bioequivalence, as an assistive tool in IVIVC [2], SUPAC, and biowaiver of BCS class I and III drugs [3]. The effectiveness of a formulation inordinately depends on the bioavailability which is the rate and extent of drug in systemic circulation that can be available at the site of action [4]. This can be easily estimated by in-vivo tests which takes in-to account valuable parameters like Cmax and AUC to estimate bioavailability[5]. In-vivo bioavailability estimation is an indispensable part of study in getting approval for New Drug Applications and novel formulations. But performing in-vivo tests to obtain bioavailability for Abbreviated New Drug Applications (ANDA) is unnecessary and it becomes a herculean task to estimate in-vivo data for large number of batches as it involves huge cost, loss of time and hindrances associated with animal ethics. Therefore, in-vivo bioequivalence is often predicted with help of in-vitro tests which follows a set of guidelines, protocols and methodology set by regulatory agencies all over the world. The USFDA has given several guidance documents on dissolution testing and acceptance criteria for Immediate Release (IR) dosage forms and also for SUPAC- IR/MR dissolution requirements. Apart from the instrumental and process parameters associated with dissolution methodology, the other most important aspects are dissolution media, the type used, volume used etc. A carefully set dissolution specifications will avoid the inconsistencies among different lots, better quality and life-cycle of product [6]. This review emphasizes on the advances in dissolution media with special focus on biorelevant dissolution media and its use in pharmaceutical industry today.

Physiological Conditions:

The absorption of drug from Gastro-Intestinal (GI) tract depends on the dissolution which depends on solubility of

drug in the gastric or intestinal fluids. The vital factors responsible for dissolution of dosage form in the lumen include the composition, volume and the hydrodynamics of the content present there. This is followed by permeability across the GI tract. Therefore, the major concern becomes the solubility of drug in GI media. This is affected by the pH and composition of media. The median pH in the upper gastric region in fasted state is 1.7 and in fed state is 5.0 in stomach [7]. Composition of contents depends on whether it is fasted state or fed state. In fasted state the gastric volume is around 15-50ml [8]it is hypo-osmotic in nature (d"200 mOsm/kg) [9], [10], with Na^+ and Cl^- being responsible. The gastric fluid has a surface tension of around 30 to 50 Nm/m, less than water(approximately70Nm/m) as reported by different researchers. Efentakis and Dressman found values of surface tension around 35-45 mN/m [11]. Finholt and Peterson in 1968 suggested through their research that the surface tension was in the range of 36-51 mN/m [12]. Pederson and his group conducted study of surface tension of gastric fluids on five healthy subjects which found surface tension in the range of 28-42 mN/m [13]. On the other hand, in fed state, the pH of gastric fluid rises and ranges from 4.3 to 5.4 [7]. Generally, the pH osmolarity and surface tension greatly depends on the type of food consumed. During fed state as the food moves towards small intestine, in duodenum the slightly alkaline secretion of liver and pancreas which is bile and pancreatic juices mix up with the chyme and raise the pH to 5.5-6.5 which is lower than that during fasted state in small intestine. There is irregular falling and rising of pH in proximal duodenum, but as the chyme moves along the small intestine fluctuations decrease. All these factors along the GI tract are responsible for modulating the solubility, dissolution and finally the rate and extent of drug absorption. In order to best mimic the in-vivo conditions to predict the behavior of solubility and dissolution inside the body, it is essential to replicate the in-vitro behavior in the best possible manner. Therefore, dissolution medias have been specified in the pharmacopoeias and by regulatory agencies so that there is similarity in dissolution testing. Though the most commonly used dissolution media has been the one specified by FDA in its guidance documents which are 0.1N HCl, pH_4.5 acetate buffer and pH_6.8 phosphate buffer which covers the pH of the GI range from pH 1.2 to 6.8, there have been other medias like simulated gastric and intestinal fluid and biorelevant dissolution media. The type of dissolution media selected as per the purpose, if it is for development purpose simulated or biorelevant media is mostly used and for quality control purposes compendial medias are used as specified by the regulatory agencies.

Dissolution media for Generic Drugs:

Dissolution methods specifications are often described in Pharmacopoeias of different countries or regions, If the product is intended to be marketed in US,

and that product is official in USP, USP specifications are followed. If the product is not official in USP, then, dissolution guidance recommended by FDA is followed. If FDA-recommended dissolution method is not available then a new dissolution method is developed which should include the pH solubility profile of the drug, dissolution in different media from pH 1.2, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. For poorly soluble drugs surfactants can be used. The FDA in its guidance document for dissolution testing of IR dosage forms has sad that, efforts should be made to perform dissolution testing in physiological conditions as it will help to interpret dissolution data with regard to in-vivo product performance. At the same time flexibility in mimicking GI environment should be allowed for and absolute adherence to maintaining GI environment in routine dissolution testing is not necessary. Dissolution test conditions should be based on physicochemical characteristics and environmental conditions the dosage form might be present when administered orally. The suggested volume of dissolution medium is 500ml, 900ml or 1000ml where sink conditions are prudent but not binding. When aqueous media are employed it should be used in range of pH 1.2 to 6.8 (ionic strength of buffers the same as in USP). While mimicking simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be utilized. Moving on to a higher pH should be reasoned appropriately depending on the case, in general, should be limited to pH 8.0. Gastric fluid should be simulated with a dissolution medium of pH 1.2 in absence of enzymes. The use of enzymes in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) should be reasoned appropriately depending on the case involved. Past knowledge through practical knowledge has indicates the need for use of (enzymes pepsin with SGF and pancreatin with SIF) to dissolve pellicles, in case formed, to allow drug dissolution. Source of water if varied and due to the active and inactive ingredients can be of a major concern leading to changes in pH and surface tension and hence water as a dissolution medium is not encouraged. For water insoluble or sparingly water-soluble drug products, use of a surfactant such as sodium lauryl sulphate is recommended [14]. The necessity for and the quantity of the surfactant should be reasoned appropriately. Use of a hydro-alcoholic medium is not encouraged. For ER and DR dosage forms similar protocol is followed for selecting dissolution media. In addition to developing any new dissolution method, dissolution profile should be generated in pH 1.2, pH 4.5 and pH 6.8. The ultimate aim should be selecting such a dissolution media which is discriminatory and replicating in-vivo physiological conditions.

Dissolution media for New Drug Applications as per US-FDA should be selected on basis of experience gained during drug development process and in-vitro performance of suitable test batches.

They should be based on acceptable clinical, pivotal bioavailability, and/or bioequivalence batches. For, New Chemical Entity (NCE), the dissolution characteristics of the drug product should be developed based on consideration of the pH solubility profile and pKa of the drug substance.

Simulated Gastric fluid (Fasted and Fed):

In fasted state as mentioned previously the median pH lies in the range of 1.5 to 1.9. The presence of pepsin and lipase becomes comparatively less significant to influence the dissolution during the fasted state. The pepsin production is 0.8mg/ml which becomes 0.08gm/ml when the drug is ingested with 200-250ml of water [15], [16]. The lipase secretion is 0.1mg/ml which on dilution again becomes less significant with the fact that it remains active only in pH range 3-6 [17]. The bile salts content in stomach in fasted state has been researched quite extensively. An average of bile salt content in stomach was found to be in range of 100-275 μM in a study conducted by Efentakis & Dressman [18] and Lindahl et al [10]. In fasted state a study conducted by Rhodes *et al.* found the bile salt concentrations upto 80μM with a standard error upto 30μM [19]. Surface tension as discussed earlier has been found in the range of 28-51mN/m. Osmolality has been found to be and reported in the range of 190-200 mosm/kg by Lindahl et al [10] and Pederson et al. [13] in their respective studies. The major cations in fasted state include sodium ion (70 mM), potassium (15 mM), chloride (100 mM) and some multivalent ions like calcium present in sub-millimolar concentrations. Depending on the physiological conditions in fasted state the composition for simulated gastric fluid in fasted state in presence of surfactant was given by Vertzoni et al. described in Table 1 [16].

Table 1. Simulated Gastric Fluid (Fasted State)

Composition	**Quantity**
HCl	0.01-0.05 N
Sodium Lauryl Sulfate	2.5 G
Sodium chloride	2 G
Distilled water q.s.	1000mL

In fed state the contents of stomach vary significantly depending on the meal consumed. Some have suggested that homogenized meal be used with a specific quantity of oil reflecting the fats present in food and co-administering with water. Then the pH, osmolarity and buffer capacity can be adjusted to best simulate the fed state conditions before the start of dissolution test in clinical studies. Apart from this, use of whole milk [20], [21] or product Ensure® [22], [23] has been suggested to mimic the fed state of stomach as it best describes the ratio of carbohydrate: protein: fat that may be present.

Simulated Intestinal fluids:

Fasted State: The buffer capacity slightly varies of fluids in fast state and fed state. In simulated fast state use of bile salts, lecithin potassium phosphate and some other components without the use of pancreatin has been given [24] in Table 2.

Table 2: SIF fasted state

Composition	Quantity
KH_2PO_4	0.029 M
Sodium Hydroxide (qs)	pH 6.8
Sodium Taurocholate	5 mM
Lecithin	1.5 mM
KCl	0.22 M
Distilled water (qs)	1000 mL

During fed state in small intestine, the meal induces secretion of more bile in small intestine which can improve the solubility of many poorly soluble BCS class II and IV drugs leading to better absorption. As buffer capacity slightly increases during fed state with decrease in pH, acetic acid has been used instead of potassium phosphate along with other components described in Table 3.

Table 3 : SIF Fed state

Composition	Quantity
Acetic acid	0.144 M
Sodium Hydroxide	pH 5
Sodium Taurocholate	15 mM
Lecithin	4.0 mM
KCl	0.19 M
Distilled water (qs)	1000 mL

Biorelevant Dissolution media development:

A constant debate over the dissolution medium to best mimic the in-vivo drug release and absorption led to the development of biorelevant dissolution media. Tremendous advances have been done in developing biorelevant media and several researchers have explored and provided compositions for biorelevant media. Biorelevant dissolution media has been primarily being used in predictions of in-vivo conditions, in developmental stages and in IVIVC correlations.

Galia et al., evaluated the effects of various dissolution media on dissolution of various BCS class I and II drugs. It was found the effects of dissolution media on dissolution of Class I drugs was not significant but greatly increased the dissolution of Class II drugs (Danazol, Mefenamic acid and Ketoconazole) in FaSSIF and FeSSIF media (Table 5) when compared with SGF, milk and Simulated Intestinal fluid without pancreatin (SIF_{sp}) [25]. Work of Vertzoni and his group highlighted the importance of simulated gastric fluid media in in-vivo dissolution of lipophilic compound GR253035X and atovaquone in fasted state simulated gastric fluid (FaSSGF), and simulated gastric fluid (SGF). GR253035X showed decreased dissolution in FaSSGF as compared to SGF_{sls} and for atovaquone dissolution was more or less limited in both media. Media composition is given in Table 4 for FaSSGF and SGF [16].

Table 4: Simulated Gastric Fluid Vs Fasted State Simulated Gastric fluid

Physicochemical Properties	**SGF**	**FaSSGF**
Sodium lauryl sulfate (% w/v)	0.25	-
Pepsin	-	0.1 mg/ml
Sodium Taurocholate	-	80 µm
Lecithin	-	20 µm
NaCl	34.2 mM	34.2 mM
Surface tension	33.7 mN/m	42.6 mN/m
Osmolarity (mosm/kg)	180±3.6	120.7±2.5
pH	1.2	1.6

Table 5: Fasted State and Fed State simulated Intestinal Fluid [25]:

	FaSSIF	FeSSIF
pH	6.5	5.0
Osmolality	270±10 mOsmol	635±10 mOsmol
Sodium Taurocholate	3.0 mM	15 mM
Lecithin	0.75 mM	3.75 mM
KH_2PO_4	3.9 g	-
Acetic acid	-	8.65 g
KCl	7.7 g	15.2 g
Sodium Hydroxide qs	pH 6.5	pH 5.0
Deionized water qs	1 L	1 L

Composition of Fed State Simulated Gastric Fluid (FeSSGF) for early, middle and late gastric conditions was suggested by Jantratid et al., to simulate postprandial conditions is given in Table 6, and an advanced prototype of Fasted State Simulated Intestinal fluid (FaSSIF-V2) was proposed with decreased lecithin and osmolality as compared to FaSSIF, and pH of 6.5 was maintained with help of maleate buffer, described in Table 7 [26].

Table 6: Biorelevant simulated FeSSGF

	Early FeSSGF	Middle FeSSGF	Late FeSSGF
Sodium chloride (mM)	147	237.02	122.6
Acetic acid (mM)	-	17.12	-
Sodium acetate (mM)	-	29.75	-
Ortho-phosphoric acid (mM)	-	-	5.5
Sodium dihydrogen phosphate (mM)	-	-	32
Milk/buffer	1:0	1:1	1:3
Hydrochloric acid/ sodium hydroxide	q.s. pH 6.4	q.s. pH 5	q.s. pH 3
pH	6.4	5	3
Osmolality (mOsm kg^{-1})	559	400	300
Buffer capacity (mmol l^{-1} ΔpH^{-1})	21.33	25	25

Table 7: FaSSIF- V2

Composition	Quantity
Sodium taurocholate (nM)	3
Lecithin (mM)	0.2
Maleic acid (mM)	19.12
Sodium hydroxide (mM)	34.8
Sodium chloride (Mm)	68.62
pH	6.5
Osmolality (mOsm/kg)	180±10
Buffer capacity (mmol/L ΔpH^{-1})	10

Ghazal et al. studied the effects of fats, protein and carbohydrates on the solubility and dissolution behavior of itraconazole where an increased solubility and dissolution was observed. Dissolution of itraconazole increased in FaSSIF media and further increased in FeSSIF media suggesting increased drug dissolution in post-prandial conditions [27]. In another study by Ghazal and his group, studied the intrinsic dissolution rate (IDR) of ketoconazole in biorelevant media. The IDR of ketoconazole varied with pH, with high IDR in pH 1.2 with decrease in IDR in SIF pH 6.8 [28]. Omuku et al., compared the dissolution of etoricoxib in different dissolution media including FaSSIF and FeSSIF and using computer simulations justified that etoricoxib could be classified as intermediate BCS class I/II rather than class II based on its solubility behavior. Though etoricoxib is a weak base no precipitation was seen during transition from low pH to high pH of biorelevant FaSSIF and SIF, indicating the role of bile salts and lecithin in aiding the drug to remain in solubilized form which suggests that during in-vivo conditions high solubility without precipitation can be expected in intestine [29]. Fagerberg et al., studied the dissolution and apparent solubility of ten BCS class II drugs in biorelevant dissolution media which led to the suggestion of upgrading five of the drugs to BCS class I category. Biorelevant media were also used to study the molecular factors like rigidity, hydrophilicity, permeability diffusivity etc. which were responsible for increased solubility in biorelevant media with help of multivariate analysis [30]. Clarysse et al., predicted that the solubilizing capacity of GI fluids might be higher than aqueous buffer systems. Clarysse et al. in another study compared the solubility of 17 model drugs in Human Intestinal fluid (HIF) with $FaSSIF_c$ and $FeSSIF_c$ and validated the same, suggesting such FaSSIF and FeSSIF can be predictive and alternative media for

intraluminal drug solubility estimation during drug discovery and early drug development phase [31]. Sachin et al., developed a novel probiotic biorelevant media which could serve as substitute to animal sacrificed based simulated colon media to test the dissolution of polysaccharide-based colon specific drug delivery. Sulfasalazine coated with different polysaccharide polymers were used to prepare spheroids that were tested in simulated colonic medium which were probiotic culture-based Fluid Thioglycolate medium (FTM), rat caecal contents, and human faecal slurries. The dissolution studies suggested no significant difference in dissolution profiles of different polysaccharide coated sulfasalazine in different media and also highlighted the benefits of simulated probiotic based FTM medium over other animal and human based colon specific dissolution medium [32].

Alhayali, Tavellin and Velaga studied the dissolution and precipitation behavior of solid dispersions of drug ezetimibe (EZ) in fasted state gastric and intestinal biorelevant media at different temperatures (25ºC and 37ºC). The study aimed at creating supersaturation of drug in intraluminal regions for enhanced absorption and bioavailability. The amorphous solid dispersions prepared by melt quenching (MQ) technique and spray dispersion (SD) techniques were evaluated for their precipitation behavior in biorelevant FaSSIF and FaSSGF and predict the in-vivo supersaturation behavior in best possible manner. The supersaturation and precipitation behavior of both formulations were temperature and media dependent. At 25ºC, the MQ was more soluble than SD of ezetimibe in FaSSIF, but at 37ºC precipitation behavior was disparate for both formulations in FaSSIF. However, in FaSSGF, irrespective of temperature the MQ gave enhanced solubility behavior than SD [33]. Madsen et al tried to establish the in-vivo supersaturation behavior of zafirlukast (ZA) in in-vitro conditions using biorelevant media in miniaturized dissolution apparatus µDissoProfiler™. Supersaturation behavior observed was disparate in different types of FedM and FastedM intestinal media. Supersaturation was of shorted time period in FedM than in FastedM, but concentration of drug dissolved during supersaturation period was higher in FastedM than FedM. Biorelevant dissolution media was able to distinguish between the effects of two polymers HPMC and PVP on supersaturation behavior of ZA, wherein precipitation of ZA was seen in FedM but not in FastedM indicating negative food effect on supersaturation of ZA in solution [34].

Some of the drug examples for which FDA guidance has been suggested or researched upon for performing dissolution in biorelevant media are;

Table 8: FDA suggested guidance, dissolution methods and research with biorelevant media

DRUGS	BIORELEVANT MEDIA	PURPOSE
Nitazoxanide [35]	Biorelevant FaSSGF Biorelevant FeSSGF Biorelevant FaSSGF-V2 Biorelevant FeSSGF-V2	Bioequivalence study
Canagliflozin (Can)/ Metformin HCl (Met) [36]	Met: Simulated Gastric Fluid [SGF] without enzyme, pH 1.2	Dissolution method
Linagliptin/Metformin HCl [36]	Simulated Gastric Fluid (SGF) without enzyme (pH 1.2) (degassed)	Dissolution method
Acetriptan [37]	Biorelevant FaSSGF Biorelevant FaSSIF-V2	Dissolution method development and Bioequivalence studies for generic version.
Furosemide (model drug) [38]	Simulated Gastric fluid Simulated Intestinal fluid	Exploring the new FloVitro™ technology
Danazol (100mg capsules) [38]	Fasted and Fed state media	In-vitro dissolution in FloVitro™ technology

Alcohol in Biorelevant Media:

It would not be fair to not consider alcohol in biorelevant media as alcohol acts as a co-solvent and helps in increasing the dissolution of most of the drugs. It is further justified by taking into account the world alcohol consumption data, as per National Institute of Alcohol Abuse and Alcoholism (NIAAA), in US approximately 56-70% of population above 18 consumed alcohol [39] and as per WHO, in Europe approximately 70% of adults consumed alcohol [40]. Alcohol and the resulting dose dumping is a serious concern incase of modified release dosage forms and abuse deterrent formulation. If the polymer or coating of MR dosage is such that it is soluble in alcohol then there are high chances that alcohol consumption

may induce dose dumping. The resulting adverse event will also depend on the therapeutic index, pharmacokinetics, etc. Taking into consideration the large population consuming alcohol and bitter history with alcohol dose dumping in a case like that of Palladone (a hydrocodone multiparticulate capsule), in 2005, led the regulatory agencies, of the European Union and United States to draw some guidance on effects of alcohol on dissolution [41]. Both agencies have given conditions of different alcohol concentrations in which dose dumping studies should be performed, Table 9. The use of alcohol (ethanol) as biorelevant media is should be on a case by case basis. It should be mandatory to test modified release dosage forms having drugs with narrow therapeutic window and with formulations of potential abuse. It also essential to consider the purpose of dissolution test whether it is to be used for quality control purpose or alcohol dose dumping studies.

Table 9: In-vitro Testing of Formulations at risk for ADD as per FDA and EMA [41].

	FDA	EMA
Requirements	Dissolution medium- 0.1N HCl Alcohol Concentrations: 0%, 5%, 20% & 40% Time- every 15mins until 2hrs	Dissolution medium: Same as that used in routine testing Alcohol Concentrations: 5%, 10%, 20%. Time: Not defined
Products to be tested	All modified release products especially opioid drugs and those having dose dumping risk	All oral modified release products

Biorelevant Dissolution Media (BDM): Future Perspectives

Biorelevant dissolution media has been majorly utilized in drug developmental studies. Its primary purpose has been to evaluate how well the drug molecule behaves in-vivo. Use of biorelevant media as a quality control tool has still not been very significantly proposed and the primary reason for it may be the increased cost and time involved in development of BDM and the consequent testing involved. All BDM have bile salts kind of surfactants added in them which can increase the solubility of poorly soluble drugs and hence sometimes fail to discriminate between experimental batches. Biorelevant media have been used in several cases to show that drug molecule

has good solubility and dissolution when characteristics when the same has failed in conventional dissolution media. The use of biorelevant media has still not found strong reasons to completely replace the conventional dissolution media, as the drug candidates which show good dissolution characteristics in conventional dissolution are obvious to show better dissolution characteristics in biorelevant dissolution media due to presence of bile like surfactants. Thus, biorelevant media surely is an essential tool to mimic physiological conditions and helpful in drug developmental stages, but its use as quality control tool to discriminate between experimental batches raises lot of questions.

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