MINI REVIEW

Role of NIB in Connecting Science to Patients by Assuring Safe and Quality Anti-diabetic Products

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ABSTRACT

In India burden of diabetes is increasing and expected to cross the 100 million mark by 2030. Therefore, development of national policies for the prevention, treatment and care of diabetes in line with the sustainable development of health care systems is the need of the hour. National Institute of Biologicals (NIB) responsibly assures and reviews the quality of Biological products to the end users by weeding out "Not-of-Standard-Quality" Biological Medicines from reaching Indian market, thereby safeguarding the Public Healthby testing at ourstate-of-art-laboratory. NIB receives samples from various sources such as State Port offices, Central Drug Standard Control Organization (CDSCO), Stakeholders of bio therapeutic manufacturers, legal & global tender samples. These are tested by pharmacopoeial methods or manufacturer's method for Key Quality Attributes (KQA). The heterogeneity of products involves human recombinant bio therapeutic Insulin, Insulin Analogues and Peptides of nearly 20 different types eg. Biphasic Insulin, Glargine, Aspart, Exenatide, Liraglutideetc. which have their global presence for the antidiabetic patient care. Testing for quality attributes such as Identification, Potency, Purity, Stability, Related Impurity and Safety parameters along with physiochemical test is carried out to ensure the safety, quality and effectiveness of the product. In addition reference standards are also being developed at NIB which serve as the measurement standards and complement the written standards in Indian pharmacopoeia. All the testing is carried out strictly adhering to the timelines so that the quality product is delivered to meet the ever-growing public health challenge

NIB maintains quality systems of ISO 17025 standards for continuous improvement, functions as Central Drugs Laboratory (CDL). It focuses on continuous supply of lifesaving bio therapeutics to ensure the success of Non-Communicable Disease (NCD) programme for Diabetes.

Key Words: *Insulin, Indian Pharmacopoeia (IP), National Institute of Biologicals (NIB)*
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INTRODUCTION

India has a challenge to face as a diabetes capital of the world with as many as 50 million people suffering from type-2 diabetes, However, medical experts feel that timely detection and right management can go a long way in helping patients lead a normal life. Diabetes might be one of the most talked about diseases across the world and especially in India, but awareness about the same can well be estimated by the fact that India today has more people with type-2 diabetes (more than 50 million) than any other nation.[1].There are approximately 70,00075,000 children with Type 1diabetes mellitus in the country[2]. Hence it becomes imperative to provide safe and effective anti-diabetics for improvement of health status of the masses.

NIB has been set up as National Control Laboratory for assuring the availability of high standard and good quality biological products for consumption in India and for exportsi.e indigenously produced and imported biological products which are forwarded to NIB for thepurposeto ensure/ordemonstrate the safety, quality and effectiveness of the product.

There are different types of insulin depending on how quickly they work, when they peak, and how long they last. Insulin is available in different strengths; the most common is U-100 Table 1[4]along with the schematic diagram Fig 1.

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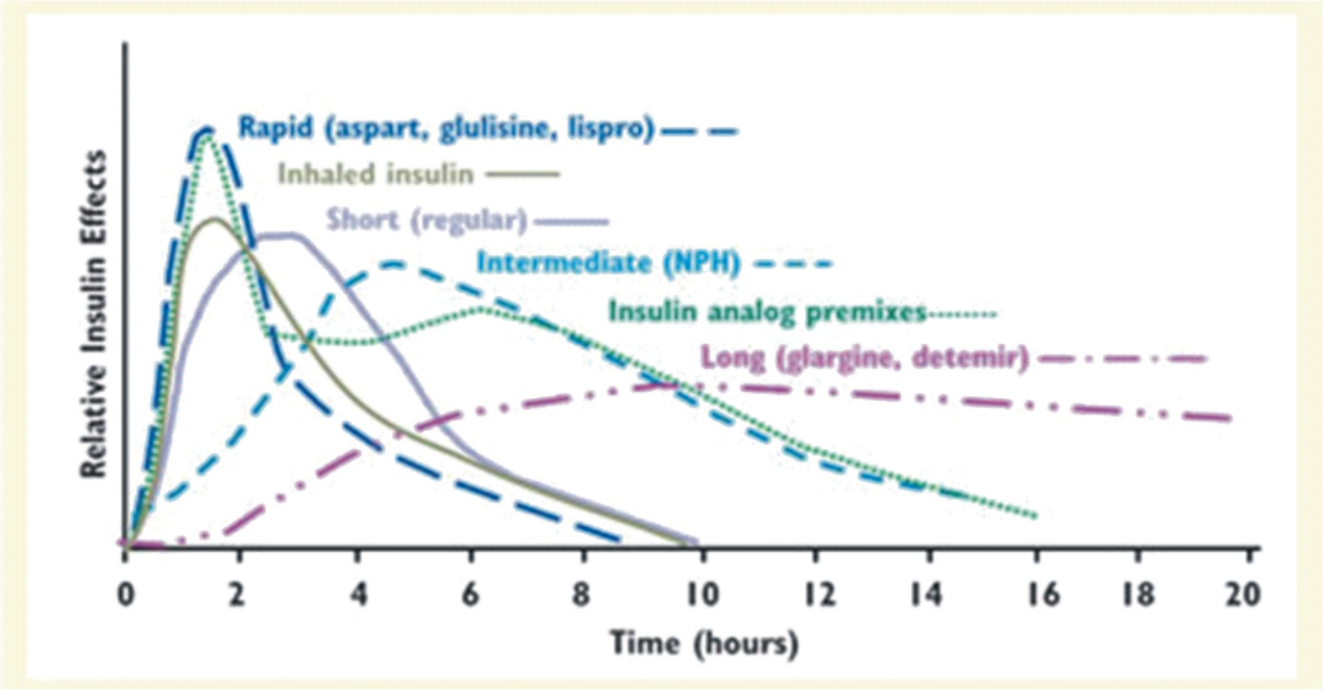
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Table 1: Insulin basics. American Diabetes Association website. Last edited 2015

Types of Insulin and How They Work				
Insulin type	Time it starts to work (onset)	Peak time	Duration it lasts	Example
Rapid-acting	About 15 minutes after injection	1 hour	2 to 4 hours	*Insulin glulisine (Apidra), insulin lispro (Humalog), and insulin aspart*
Short-acting, also called regular	Within 30 minutes after injection	2 to 3 hours	3 to 6 hours	*Huminsulin R*
Intermediate-acting	2 to 4 hours after injection	4 to 12 hours	12 to 18 hours	*NPH (Huminsulin N)*
Long-acting	Several hours after injection	Does not peak	24 hours; some last longer	*Insulin detemir (Levemir) and insulin glargine (Lantus)*

Fig1: Schematic presentation of Insulin profile.



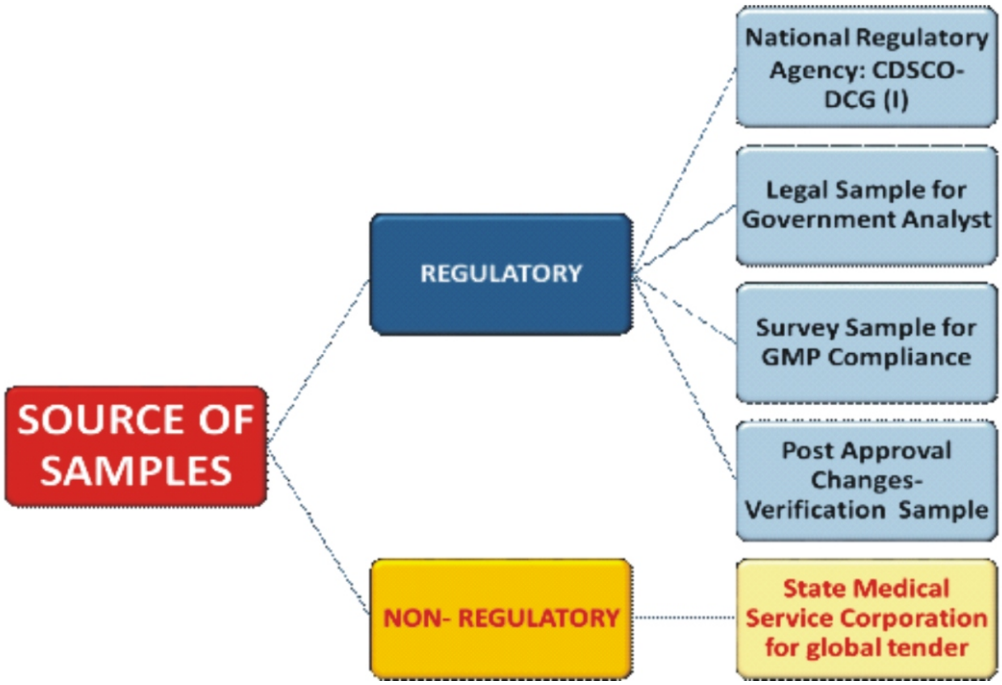
Source: US Pharm. 2007; 32(10)(Diabetes suppl):10-16.

Need for Quality Control:

Quality Control Tests ensures safety and therapeutic activity of formulations whose performance is consistent and predictable. Testing for quality attributes such as Identification, Potency, Purity, Stability, Related Impurity and Safety parameters along with physiochemical test is essentially carried out. All the testing is carried out strictly adhering to the timelines so that the quality product is delivered to meet the ever-growing public health challenge.

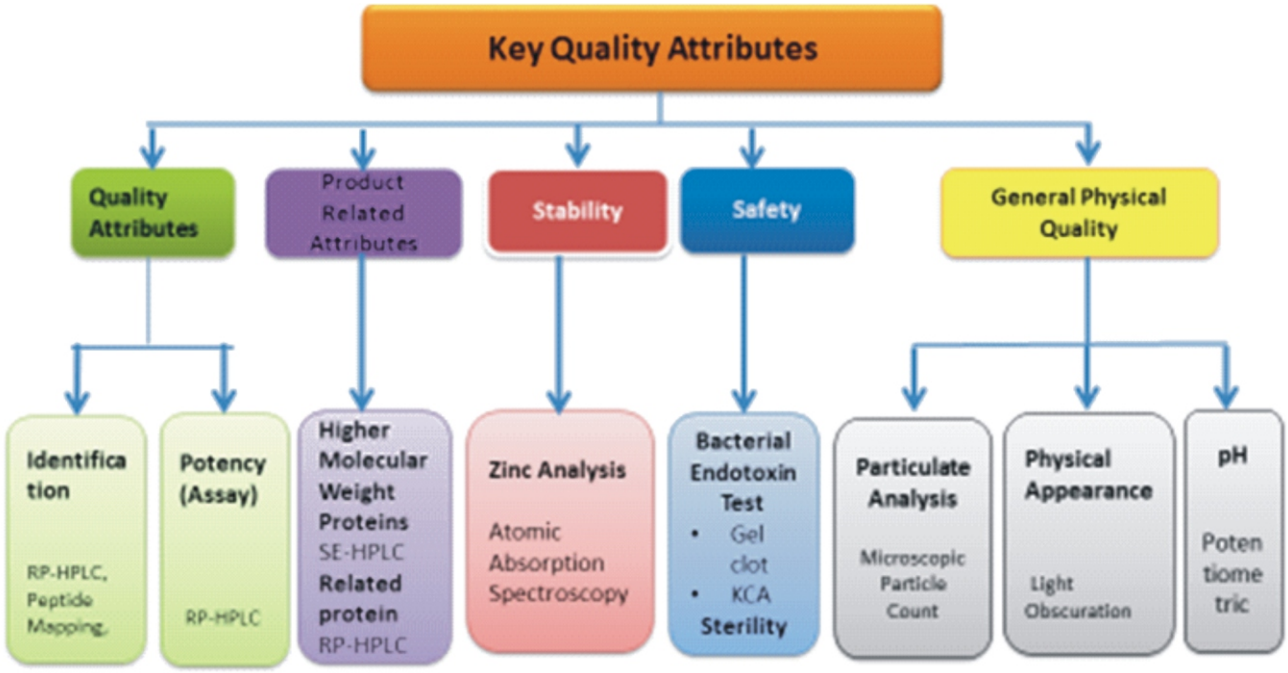
NIB receives samples from various sources such as State Drugs/ Port offices, CDSCO(domestic manufacturers or imports), legal & global tender samples (Fig 2)

Fig 2: Samples received from various sources



They are tested by pharmacopoeial methods or manufacturer's method for Key Quality Attributes (KQA).Appropriate methods and documented procedures for all QC tests under Identification, Potency (efficacy), Safety, Purity and Physiochemical quality are carried out by the lab to assure that the products meet standards appropriate for their intended use.(Fig 3)

Fig 3: Various QC tests carried out for Identification, Purity, safety and general physical quality.



The heterogeneity of products involves human recombinant bio therapeutic Insulin, Insulin Analogues and Peptides of nearly 20 different types e.g. Biphasic Insulin, Glargine, Aspart, Exenatide, Liraglutideetc. which have their global presence for the antidiabetic patient care.[3]

To assure the quality of test results NIB laboratories have quality control procedures for monitoring the validity of tests [5]. Each test parameter is performed as per the specification given in the pharmacopoeia. It is imperative that the potency falls in the specified range indicating that the drug is efficacious. As the products are recombinant in nature, testing for purity parameter namely presence of Related Proteins and High Molecular Weight Proteins (HMWP) becomes imperative. The test values for these products when within the limits indicate that the recombinant samples have been properly stored hence ensures good quality of the product till its shelf life. Similarly, related impurities when fall within the specification limits indicates that samples are intact and not going to degrade till its shelf life.Confirmation for the quantity of Zinc metal ion content is equally important as Zinc in pancreatic beta cells binds to several insulin molecules, six to be exact, forming what's called an insulin hexamer for storage. In fact, long acting insulin formulations for injection for eg NPH or Lantus, contain zinc so that the insulin is bound in hexamers that convert to the active insulin monomer (a single insulin molecule) slowly.

Safety tests performed for parenteral preparation are: sterility by membrane filtration method and Bacterial Endotoxin Test (BET). Sterility or freedom from presence of viable microorganism is strict, uncompromising requirement of an injectable dosage form. Test for Physical quality under parenteral include: color/clarity/appearance, particulate analysis by light obscuration or microscopic method and pH determination which also have to be complied. The resulting data is recordedin a way that the trends are detectable and where practicable, statistical techniques are applied in reviewing of results. This monitoring is planned and reviewed which includes regular use of certified reference materials, participation in Interlaboratory comparison programmes.[5]

NIB is complying with the standards of ISO/NABL IEC 17025:2005, demonstratingthat it is technically competent and able to produce precise and accurate test and/or calibration data.

NIB also functions as Central Drugs Laboratory (CDL) with various rolesuch as statutory functions like analytical quality control of majority of the imported Drug available in Indian market as well as manufactured within the country.

Way Forward:

The annual expenditure on account of diabetes treatment in India is packed at Rs 1.5lakh crore. Thus it becomes need of the hour to provide safe, effective and good quality product to the end user. NIB is complying with the standards of ISO/NABL IEC 17025:2005 in assuring the quality of test results which assures competence of the lab and analyst and gives a recognition worldwide with the global standard setting agencies. NIB responsibly assures and reviews the quality of Biological products to the end users by weeding out “Not-of-Standard-Quality” Biological Medicines from reaching Indian market, thereby safeguarding the Public Healthby testing at ourstateof art laboratory.

With many expensive and high-selling biologicals losing patent protection and other exclusivity rights, biosimilar of these molecules may now enter the market, resulting in a shift of market shares, revision of strategies of companies and attraction of new players to the biopharmaceutical market. Hence it becomes imperative to assure that there is a continuous supply of lifesaving bio therapeutics. A set of tests and acceptance criteria are established based on recombinant products characterization and prevalent regulatory requirements in order to ensure drugquality. NIB also has a mandate of preparing National Reference Standards by the way of conducting Inter laboratory collaborative study. It is well known that reference standard remain fundamental to ensuring the quality of biological products as well as the consistency of production.(6)This will aid the manufacturers of the Insulin analogues who are at the developmental stages to use this reference standard for comparison of their test results and to provide regulatory limits.In addition reference standards are also being developed at NIB through a collaborative approach, which serve as the measurement standards and complement the written standards published in Indian Pharmacopoeia.[7]. NIB also through constant support to the stakeholders enhances the capacity building at their developmental stages as well as developmental stages. It is to mention that Quality

Control is essential in the drug manufacturing to ensure that the drug substances and other raw material are suitable for use in drug product and to ensure that the drug product manufactured meets highest quality standards. Quality Control tests ensure safety and therapeutic activity of formulation whose performance is consistent and predictable.

Conflict of interest : Nil

Financial Sources : Nil

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