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SIGNIFICANCE OF PHARMACEUTICAL FACTORS ON SELECTION OF BIOBATCH

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ABSTRACT: Biobatch is usually prepared for the purpose of pharmacokinetic evaluation before NDA or IND filing. There are several critical issues that one has to face during the audit process like equivalence between the Biobatch and proposed commercial production batch. During the development and scale-up of the manufacturing process, various standard operating processes have to be documented to provide link between the bio/clinical batch and commercial batch. The Biobatch is a key component of the quality assessment, regardless of whether there is a biowaiver supported by dissolution studies or a formulation comparison, or bioequivalence study. *IVIVC* is one of the methods accepted by regulatory authorities including USFDA and it is applied while preparing the Biobatch. Extensive pilot experiments are to be carried out before a Biobatch is prepared. This may increase the cost of production for the company. Further, even after the approval of the formulation, various pharmaceutical factors may vary and lead to inconsistencies during the production phase. Recently, to overcome these problems, several software is available. Judicious use of the comprehensive software coupled with suitable *in-vitro* testing may provide an economical solution for the preparation of a Biobatch. Among various software 'Gastroplus' is one of the best software that predicts the absorption pattern, pharmacokinetics, and pharmacodynamics for drugs administered via intravenous, oral, ocular, and pulmonary routes in human and preclinical species and may become must alternative for Bio studies.

INTRODUCTION: As per the WHO Biobatch is defined as the test batch used in the bio study to demonstrate bioequivalence, or used in the bio wavier to demonstrate similarily, as compared to the innovator product [1]. It is required for the purpose of submission to the regulatory authorities for either biowaiver or conducts BA/BE & clinical trial.

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The Batch should be 10% of the proposed maximum commercial production batch or at least 100000 units whichever is greater [2]. Bio wavier is the condition wherein drug developers and generic companies get an exemption from carrying out the bioequivalence studies from the regulatory authorities. Compounds that are classified as Class I of the Bio-Pharmaceutics Classification System are eligible for the biowaivers because the rate and extent of the drug absorption of such compounds not likely to be affected by drug dissolution and /or GI residues time, and *in-vivo* bioequivalence studies (for new formulation, *etc*.) may be waived based on *in-vitro* permeability and solubility data [3].

Biobatch is also called a Biological evaluation batch which is prepared for conducting clinical trial

in NDA or ANDA application. After drugs successful preclinical toxicity and pharmacokinetic studies the drug has to be taken to the phase I clinical study because biological evaluation is necessary to prove efficacy and safety of drug in human body. Bioequivalence studies are normally required to be done for every new generic product in that test product tested against the innovator's marketed product [4-5]. Bioequivalence is also required when the proposed marketed dosage form is different from the used clinical trial or when significant changes are made in the manufacture of the marketed formulation [6].

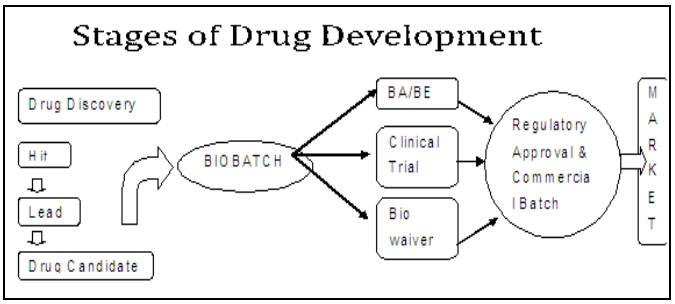

FIG. 1: STAGES OF DRUG DEVELOPMENT AND BIOBATCH

Preparation of Biobatch is a great challenge. It has to meet various parameters related to quality assessment from a regulatory point of view. The manufacturer has to be careful to develop both production batch as well as the Biobatch. Biobatch is, in fact, a representative of production batches having the same formulation and same manufacturing process with respect to equipment, process and controls and hence a subject of regulatory audit at every step.

Pharmaceutical development data, of Biobatch, represent key information that is used throughout the quality assessment. To evaluate the critical control parameters and one requires details of unit operation, control analysis techniques and by fractional factorial designs are often used to challenge the tentative control limits established for the process at different stages.

After the regulatory submission of IND, NDA or ANDA application there are Pre- Approval Inspections conducted by FDA where sampling and analysis of the Biobatch are audited. There are audit of the raw data for its integrity, in-process and finished product testing records and specific product and process of Biobatch preparation. During ANDA approval audit Biobatch is compared with marketed batch including the field commercial process.

Significance of Bioequivalence in Preparation of Biobatch: There are several critical issues that one has to face during the audit process like equivalence between the Biobatch and proposed commercial production batch. If there are any differences it has to be discussed with regard to the potential impact on product bioequivalence [9].

Therefore it is important that during the development and scale-up of the manufacturing process, it has to be well documented so that a link between the bio/clinical batch and commercial batch can be established.

When there is Bio wavier, the Biobatch (BW or BE batch) is of prime importance to support the dossier with respect to bioavailability and Bioequivalence. Bioavailability of a drug depends on various factors like route of administration and pharmaceutical factors and condition of the patient. There are several physiological steps which directly affect the bioavailability of drug when it is administered through oral route. The systemic absorption of an orally administered drug in a solid dosage form comprising of three distinct steps: the disintegration of the drug product; dissolution of the drug in the fluids at the absorption site and transfer of drug molecule across the membrane lining the gastrointestinal tract into the systemic circulation.

For the therapeutic effect of an orally administered drug it must be absorbed in systemic circulation so that any factor that affects any of these three steps can alter the drug's bioavailability. Hence, its therapeutic effect in the clinical trial may not match with the comparator drug/within regulatory requirement so bio batch selection is also important before conducting a clinical trial.

Patient-related factors can change the bioavailability of drug, and there may be patient to patient variation in results of bioavailability so Biobatch may not be dependent on such uncontrolled factors. The same thing may happen because of the influence of route of administration on the bioavailability of drug.

Pharmaceutical Factors in Biobatch: Pharmaceutical Factors in a Bio Batch may be Formulation Related Factor or Technological Related Factor.

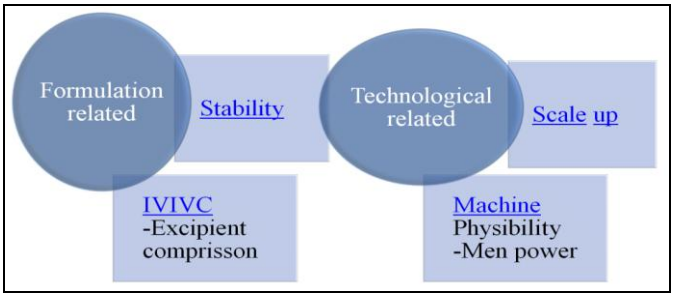

FIG. 2: FACTORS AFFECTING BIOBATCH SELECTION

Formulation Related Factors are involved in the manufacturing process. They include several steps and parameters as mentioned in the Ishikawa diagram **Fig. 2** for tablet manufacturing. Here, Plant factor, Compressing, Drying, Granulation, Raw Materials, and Analytical Methods have own importance in tablet quality and uniformity threw out manufacturing.

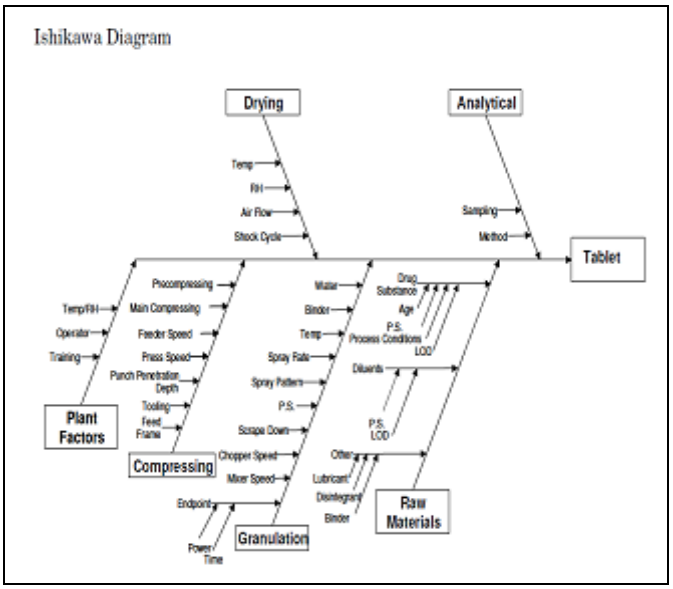

FIG. 3: ISHIKAWA DIAGRAM FOR DIFFERENT FACTORS AFFECTING DURING TABLET MANUFACTURING [11]

As it can be seen from the Ishikawa diagram, there can be a large number of variables. Any of these variables can change the dissolution profile hence, bio batch result may vary and batch uniformity may not be maintained. To maintain the batch uniformity and drug quality good manufacturing practice (GMP) and good laboratory Practices (GLP) guidelines have to be followed in the Research and Development laboratory. There are guidelines available for GMP issue and by WHO and USFDA, It is mentioned that there must be standard operating procedure (SOP) for each process. For example in tablet manufacturing process during granulation mixer speed, chopper speed, temperature, spray rate, water concentration can make the difference. Thus, there is a need to follow SOP at each step and they should be updated as per the development into the process. During development of SOP, design of experiment (DOE) is also applied for optimization process and design space needs to be generated such that when any change is made, the drug uniformity is not affected.

Similarly, a change in any variable for the dissolution profile of the drug would affect the pharmacokinetics of the formulation. If drug is dissolved as per the time required or contains similar profile as reference drug than pharmacokinetic profile of drug might be within the acceptable limit. From the dissolution profile drugs pharmacokinetic parameter can be predicted using *in vitro* and *in vivo* Correlation ship (IVIVC). In vitro dissolution study is planned on the basis of human physiology so that better predictive result can be obtained.

Dissolution Testing in Biobatch: Dissolution testing is usually recommended as per USFDA guidelines. The dissolution methodology is developed, after setting specifications as per the regulatory requirements.

- Dissolution testing of immediate-release solid oral dosage forms [12];
- Extended-release oral dosage forms: development, evaluation, and application of *in-vitro/in-vivo* correlations.

As per guideline the dissolution profiles, at least 12 individual dosage units from each lot should be determined. A suitable distribution of sampling points should be selected to define adequately the profiles. The coefficient of variation (CV) for mean dissolution profiles of a single batch should be less than 10%. Dissolution profiles are to be generated at different agitation speeds (*e.g.*, 100 to 150 revolutions per minute (rpm) for U.S. Pharmacopeia (USP) Apparatus I (basket), or 50 to 100 rpm for USP Apparatus II (paddle)) [12]. The pH

solubility profile of the drug is also important during dissolution test.

Importance of Dissolution for IVIVC: *In-vitro* dissolution testing is an important test for, providing process control and quality assurance; determining stable release characteristics of the product over time; and facilitating certain regulatory determinations (*e.g.*, absence of effect of minor formulation changes or change in manufacturing site on performance). In certain cases, especially for extended-release formulations, the dissolution test can serve not only as quality control for the manufacturing process but also as an indicator of how the formulation will perform *in-vivo*.

Bioequivalence is established between the generic product and the reference listed product at the highest and lowest strengths. For the reference listed product, all strengths are compositionally proportional or qualitatively same and have the same release mechanism, and the in vitro dissolution profiles are similar.

As per the regulatory requirements of ANDA application for biosimilar drug, if the dissolution profile of test drug would match with the reference drug than BA/BE study would not be required. Thus, dissolution is very important parameter of drug not only as Quality Control purpose but also for research and drug efficacy it is very important. More queries may be expected during evaluation of dossier by FDA or during audit if the dissolution results are not supported by scientific justification. To control those queries Quality by Design (QbD) has to be implemented. QbD principles are applied in manufacturing or analytical testing like dissolution.

Stability Studies of Biobatch for its Equivalence: A key component of process validation may show clinical or bio-batch equivalence. It is a frequent matter of discussion for all solid dosage form compliance inspection since raw material variation can cause final product variation in uniformity, disintegration, hardness (tablets), and dissolution. It is desirable to use the same dosage form (tablet or capsule) for commercial batches as that used for Biobatches. This facilitates comparison of in-process testing result from validation batches to the bio- batches. Historically early R & D batches have utilized dry filled hard gelatine capsule for convenience if it differs from the final commercial dosage form.

To have a full-scale production sufficient data should be collected during the bio-batches so that a comparison can be made with the full-scale demonstration batches or validation batches. Statement of equivalence is usually made by taking in to account the in-process results, raw material testing result, and final product testing. It may be part of the validation report or in the conclusion of development report that includes the full-scale data.

As per the ICH Q1A (R2) recommendations, three primary batches of at least of the pilot-scale sizes for the drug substance are filed in the DMF. These batches should be made under current good manufacturing practice (cGMP). Once a laboratory batch (often called 1X) has been determined to be both physically and chemically stable based on accelerated, elevated temperature testing (*i.e.* 1 month at 45 C or 3 months at 40 °C or 40 °C/ 80% RH), the stability guidance recommended a minimum of 6 months of accelerated data and 6 month of long term data for pilot scale batches are to be submitted initially in the DMF to support ANDA application.

Additional long term data for all three batches should be submitted as an amendment. The testing time period for the accelerated storage condition has to include, a minimum of three-time points including initial and final time points (*e.g.* 0, 3 and 6 months). For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed retest period of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed retest period [13].

Significance of IVIVC in Biobatch: IVIVC (a predictive mathematical model describing the relationship of drug between an in-vitro property of a dosage form and an *in-vivo* response), is one of the methods accepted by regulatory authorities including USFDA. The purposes of application of

IVIVC for biobatchis is reduction of regularity burden, optimization of formulation, justification for "therapeutic" product quality and quality control test for scale-up and post-approval changes sometimes and cost-saving during the product development. It works as surrogate for *in-vivo* bioequivalence and to support bio waivers (time and cost-saving).

Thus, the main objective of developing and evaluating an IVIVC is to establish the dissolution test as a surrogate for human bioequivalence studies, which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and post-approval changes. However, for the applications outlined in ANDA, the adequacy of the in vitro dissolution method acts as a surrogate for in vivo testing should be shown through an IVIVC for which predictability has been established.

The expectations from IVIVC depend on the nature of drug based on BCS classification.

TABLE 1: *IN-VITRO IN-VIVO* CORRELATION POSSIBILITY IN BIOLOGICAL CLASSIFICATION SYSTEM [18]

Class	Solubility	Permeability	Absorption rate control	IVIVC expectation
BCS Class I	High	High	Gastric empty	IVIVC expected if dissolution rate is slow than gastric emptying rate otherwise limited or correlation
BCS Class II	Low	High	Dissolution	IVIVC expected if *in -vitro* dissolution rate is similar to *in-vivo* dissolution, unless very high dose
BCS Class III	High	Low	Permeability	Absorption (permeability) is rate determining, limited or no IVIVC with dissolution
BCS Class IV	Low	Low	Not defined (case by case)	Limited or IVIVC is expected

Based on regulatory guidelines, the *in-vitro* profiles are regarded acceptable for an IVIVC if the dissolution rate is a mean of twelve individual determinations and the coefficient of variation at each sampling point is less than 10%; however the initial release data may exhibit a larger variability [17].

***IVIVC* Established by Two Models for BioBatch:** *IVIVC* for any dosage form can establish by two models (1) Convolution model and (2) Deconvolution model. Convolution is the process of drug in the body to reflect blood drug concentration-time profile (right to left). On the other hand, extracting dissolution profiles from blood drug concentration-time profile is known as Deconvolution process (left to right).

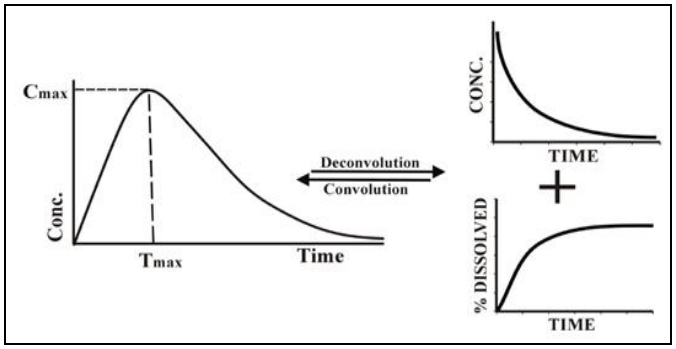

FIG. 4: SCHEMATIC REPRESENTATION OF DECONVOLUTION AND CONVOLUTION PROCESS [18]

It means in the development of the convolution model the drug concentration-time profile obtained from dissolution results may be evaluated using criteria for *in-vivo* bioavailability / bioequivalence assessment, based on C max and AUC parameter.

Deconvolution is a numerical method used to estimate the time course of drug input using a mathematical model based on the convolution integral. The Deconvolution technique requires the comparison of *in-vivo* dissolution profile which can be obtained from the blood profiles.

The observed fraction of the drug absorbed is estimated based on the Wagner-Nelson method or Loo-Riegelman. After optimizing the suitable model for Bio Batch evaluate the batch for prediction of the *in-vivo* result by applying different method.

There are three types of *IVIVC* Correlation are established [15, 18] (1) Level A correlation: One to one relationship between *in vitro* and *in-vivo* data, *e.g.*, *in-vitro* dissolution *vs. in-vivo* absorption. (2) Level B correlation based on statistical moments, *e.g.*, *In-vitro* MDT *vs. in-vivo* MRT or MAT (3) Level C correlation means to point relationship between a dissolution and a pharmacokinetic parameter, *e.g.*,

in-vitro T50% *vs., in-vivo* Tmax, Multiple C: relationship between one or several PK parameters and amount dissolved at several time points. In selection of BioBatch Level an *IVIVC* is considered to be the most informative and is recommended, if possible to establish. Level C correlations can be useful in the early stages of formulation development when pilot formulations are being selected but Level B correlations are least useful for regulatory purposes.

Establishment of Level an IVIVC in BioBatch: The most commonly seen process for developing a Level An *IVIVC* is to (1) Develop formulations with different release rates, such as slow, medium, fast, or a single release rate if dissolution is condition independent; (2) obtain *in-vitro* dissolution profiles and *in-vivo* plasma concentration profiles for these formulations; (3) Estimate the *in-vivo* absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (*e.g.,* Wagner-Nelson, numerical deconvolution). These three steps establish the *IVIVC* model. Alternative approaches to developing Level an *IVIVC*s are possible.

Methods for Evaluation of IVIVC model of BIOBATCH for Predictability: [19] All *IVIVC* model of BioBatch should be studied fist using internal predictability method. One recommended approach involves the use of the *IVIVC* model to predict each formulation's plasma concentration profile (or C and/or AUC for max a multiple Level C *IVIVC*) from each respective formulation's dissolution data. This is performed for each formulation used to develop the *IVIVC* model. The predicted bioavailability is then compared to the observed bioavailability for each formulation and a determination of prediction error is made. An acceptance criterion for internal predictability is the average absolute percent prediction error (% PE) of 10% or less for Cmax and AUC establishes the predictability of the *IVIVC*.

In addition, the % PE for each formulation should not exceed 15%. If it was not satisfied than the internal predictability of the *IVIVC* is inconclusive. Another method is external predictability which is most important when using an *IVIVC* as a surrogate for bioequivalence. It gives them confidence that the *IVIVC* can predict *in-vivo* performance of subsequent lots of the drug product. Therefore, it may be important to establish the external predictability of the *IVIVC*. This involves using the *IVIVC* to predict the *in-vivo* performance for a formulation with known bioavailability that was not used in developing the *IVIVC* model. Acceptance criteria for external predictability result for BioBatch were % PE of 10% or less for C and AUC establishes the external max predictability of an *IVIVC*. % PE between 10 - 20% indicates inconclusive predictability and the need for further study using additional data sets.

Results of estimation of PE from all such data sets should be evaluated for consistency of predictability. % PE greater than 20% generally indicates inadequate predictability, unless otherwise justified. With the exception of narrow therapeutic index drugs, the external predictability step in the *IVIVC* evaluation process may be omitted if the evaluation of internal predictability indicates acceptable % PE.

However, when the evaluation of internal predictability is inconclusive, evaluation of external predictability is recommended.

Pharmacokinetic Software's Use in BioBatch: There are several Pharmacokinetic software which is available to guide the scientist for preparation of BioBatch at every stage **Table 1**. This software provides the result on human Physiology based pharmacokinetic (PBPK), applied Principle of Bayesian estimation, *in-silico*, and *IVIVC* data. When new drug molecule is developed at that time acslXtreme and DDI Predict software help to give drug-drug interactions result between a drug candidate and a large panel of marketed or withdrawal drugs.

BioBatch statistical analysis for bioavailability and Bioequivalence studies with the help of BIO PAK software. There are different software like Bear, ATIS like which gives nonlinear regression and optimal sampling technique for clinical studies. They also analysis average bioequivalence data from non-compartmental analyze the ANOVA for crossover or repeated crossover design. Some software analyze average bioequivalence involves the calculation of 90% confidence intervals for the

ratio of the measures for the test and reference products.

Gastropubs like software predict the pharmacokinetic profile as per route of administration of drug. For generic drugs APIS like software helps to give pharmacokinetic data based on previous study patient information (population) to determine patient-specific parameter estimate. From the different batches to select the BioBatch which had pharmaceutical stability can evaluate on Stab for R software. There is some software which also gives rapid analysis and understanding of the behavior of drug candidates in animal and human. Some software also gives food effect and effects of influx and efflux transporters in gut or any tissue. They also predict biopharmaceutical properties from chemical structure and also tracks multiple metabolites formed into body. The software predicts steady-state and dynamic drug-drug interaction.

TABLE 2: SOME OF THE PHARMACOKINETICS SOFTWARE WORKS IN FOLLOWING WAYS LIKES

S. no.	Software Name	Manufactured by	Uses
1	acslXtreme	A Egis Technologies Group	Provides physiology-based pharmacokinetic (PBPK) and pharmacodynamic (PD) simulation software for the pharmaceutical research and development process, It helps to develop predictive models of the new and potential drug product
2	APIS	A. Iliadis and M. Laplane	It is based on mathematical modeling and helping in optimizing therapy. This software incorporates the principle of Bayesian estimation, *i.e.*, one can use all available patient information (population) to determine patient-specific parameters estimate
3	AUC-RPP	W. A. Ritschel	Non compartmental evaluation for pharmacokinetic parameter
4	ADAPT II	D. Z. D'Argenio and A. Schumitzky	This program performs simulations, nonlinear regression, and optimal sampling
5	ATIS	T. Amiskai	Non linear least square
6	Bear	Hsin-ya Lee and Yung –jin Lee	It was designed to analysis average bioequivalence data from non-compartmental analysis to ANOVA for crossover or repeated crossover design. It also analyzes average bioequivalence and involves the calculation of 90% confidence intervals for the ratio of the average of the measures for the test and reference products. The BE will be conducted based on the calculated 90% CIS
7	BIOEQV52, BIOPAR40, and BIOEQNEW	H. P. Wijnand	Perform bioequivalence calculation including statistical power
8	BIO PAK	SCI software	Statistical analysis package for bioavailability/ bioequivalence studies
9	Calcu Syb		For Windows is an analyzer of combined drug effects, able automatically to quantify phenomena such as synergism and inhibition
10	DDI Predict	Aureus Sciences	Provides an instant graphical report contain all potential drug-drug interactions between a drug candidate and a large panel of marketed or withdrawal drugs. The predictions are based on the plasma concentration of the drug candidate in the presence or absence of enzyme inhibitors
11	GastroPlus	Simulation Plus	It is physiology-based software program that simulates intravenous, oral, oral cavity, ocular, intranasal, and pulmonary absorption, pharmacokinetics in human and animal. Using in silico/ in vitro data with our whole body PBPK models to predict first-in-human or animal outcomes, conduct virtual population trials, fit a wide variety of model parameters for single or multiple data sets, understood food effects, assess the impact of non linear metabolism or transport, track metabolites formed in any tissue analyze various formulation strategies, generate in vitro-in vivo correlations (IVIVC), and predict drug-drug interaction (DDI)
12	Stab for R	Hsin-ya Lee and Yung-jin Lee	It was designed to analyze pharmaceutical stability data. They follow 'ICH Q1E Evaluation for stability data' (from USFDA site) to design this tool

CONCLUSION: Biobatch is very important in Drug Discovery and Regulatory Application for IND, NDA Approval. It is also very important after getting approval for future scale-up and Post-approval changes and as a substitute for studies by establishing IVIVC correlations. Biobatch quality

is most important for drug discovery and drug design. Biobatch stability data and validation documentation are also important for audit purpose and product uniformity. Use of IVIVV and pharmacokinetic software is also helpful in clinical trial batch selection and decrease in the clinical trial rejection. It also very important for faster FDA Review process by applying DOE and QbD approach for manufacturing Biobatch.

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CONFLICT OF INTEREST: Nil

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