nextar
chempharma solutions

Key Technical Considerations During Development

Dr. Orna Dreazen

CEO and Chairperson of the Board of Directors at Nextar

Dear inventor,

We appreciate your great idea. Nextar's team would like to be your partner on your journey, of realization of your idea into a biopharmaceutical product/medical device. This technical document was created in order to assist you on your way and outline the needs that may arise and may be provided by us to increase the chances of success and shorten the time and resources invested in making your dream come true.

Table of Contents

About Nextar

Nextar's Profile

Nextar Chempharma Solutions Ltd. Is a one-stop-shop outsourcing company providing full integrated contract drug development and manufacturing services. We brought together industry's leading scientists and highly-reputable R&D and production teams to support our customers with strong expertise in cutting edge technologies. Our professional and experienced team can significantly shorten your development and manufacturing timelines by:
Offering a large portfolio of services

- Operating from its modern 1400 m2 state-of-the-art labs, clean rooms & equipment
- Providing services by experienced high-skilled professional teams (provided services to more than 150 companies)
- Advising you regarding regulatory requirements and avoiding unnecessary work
- Holding cGMP, ISO13458, ISO9001 and GLP worldwide recognized certifications, from regulatory agencies

Services & Capabilities

Nextar's mission is to provide sponsors with high-quality, cost effective, reliable and integrated chempharma solutions, offering its customers flexible access to a full range of chemical, production and analytical services including:

- Custom chemical synthesis, separations and extractions (non GMP)
- Formulation development of all types of dosage forms, injectables, topical creams, ophthalmic solutions, suspensions, emulsions, liposomes, lyophilized formulations, capsules, tablets, slow-release formulations
- Analytical and bio-analytical assay development and validation
- Stability studies at all desired and accelerated conditions
- Supply of test articles for preclinical toxicity studies (GLP)
- *In vitro* GLP studies (preclinical work)
- Bioanalytical studies in serum and tissues

- Contract GMP manufacturing, packaging and labeling of Clinical Trial Materials (liquids, semi solids and lyophilized products).
- Preparation of Chemistry, Manufacturing and Control (CMC) documentation and support for regulatory submission
- Quality Assurance (QA) consulting services

Dr. Orna Dreazen, Chairperson of the Board of Directors and CEO.

Dr. Orna Dreazen holds a Ph.D in Biochemistry from the Weizmann Institute of Science. Her postdoctoral studies were completed at University of California in Los Angeles. In 1994 she got a diploma in Business administration from the Tel Aviv University. Dreazen served in key positions in the Industry as well as a public servant: She was the Quality control manager of Interpharm Laboratories Ltd., Established a start up biotech company, Portman pharmaceuticals Ltd. Between 1994 and 2000, she was the General Director of the National Public Health Laboratories of the Ministry of Health and between 2000 to 2008 she served as the General Director of the Israel Laboratory Accreditation Authority. In this capacity, she was involved in many international activities such as, taking an active role as a member in the Board of Director of the International Laboratory Accreditation Cooperation (ILAC), The Arrangement Committee Chairperson, representing ILAC in ISO and WHO, and The Bureau International Poids and Measures (BIPM) managing the metrology, weights and measures around the world. Dr. Dreazen is an expert in Quality and Metrology and was the Chairperson of the Israel Society of Metrology.

Daniel Epstein, Ph.D - Director of Analytical Labs

Dr. Daniel Epstein holds a Ph.D. in chemistry from the State University of New York at Buffalo. He brings with him 10 years of experience in analytical chemistry in the pharmaceutical industry. Before joining Nextar Dr. Epstein worked as a Study Director at Analyst Research Laboratories where he gained extensive experience in analytical and Bioanalytical methods development, validation, and implementation. In his capacity as Study Director he oversaw the performance of up to 20 GLP studies annually from development to the successful analysis of thousands of

biological samples. Dr. Epstein brings with him a broad knowledge of analytical instrumentation encompassing all aspects and stages of drug development.

Batia Ben-Aroya, Ph.D - Head of Chemistry and Production Director

Dr. Ben-Aroya holds Ph.D. in Organic Chemistry from Tel-Aviv University, Israel. Dr. Ben-Aroya recently returned from a post-doctoral position in the University of British Columbia (UBC), Vancouver, Canada. At UBC, she was working in the Advanced Biomaterials laboratories in the forestry department, where she was responsible for the organic synthesis projects. Dr. Ben-Aroya specialized in the synthesis and design of composite biomaterials and has developed methods and techniques for casting these novel biomaterials into honeycomb shaped thin films. During her Ph.D. Dr. Ben-Aroya has specialized in Solid Phase Organic Synthesis of small molecules, combinatorial chemistry and high-throughput synthesis. She is proficient in organic synthesis and analysis, including chromatography (HPLC, GPC, GC-MS), UV-vis and FTIR spectroscopy, thermal analysis (MDSC, MTGA), elemental analysis and highly experienced in various NMR techniques (1D, 2D techniques and gel phase NMR). Dr. Ben-Aroya brings to the company many years of experience in organic chemistry.

Alex Krol, Msc. - Director of Analytical R&D

Mr. Alex krol holds a Msc. in organic chemistry from the University of Ivanovo State University of Chemistry and Technology (ISUCT). He brings with him 17 years of experience in analytical chemistry in the pharmaceutical industry. Before joining Nextar Mr. Krol worked as a 6 years at Analyst Research Laboratories where he gained extensive experience in analytical and Bioanalytical methods development, validation, and implementation. Alex brings with him a broad knowledge of analytical instrumentation, Analytical and bioanalytical methods development by HPLC/PDA/CAD/ ELSD/Fl , GC FID /MS and LC/MS/MS, Characterization of known and unknown compounds,

Purification and identification of impurities, Evaluation of extractables and leachables from product-contact materials.

Recent Successful Case Studies Outsourced to Nextar

- Lyophilized peptide formulation with increased stability and safety
- Formulation development and GMP manufacturing of freezed-dried vaccine formulation with a very limited amount of API
- Repositioning of a generic drug as a slow release tablet formulation with improved pharmacokinetic profile for new indication
- Successful taste masking of oral anticancer cocktail formulation containing bitter drugs
- Formulation of water-insoluble anticancer drug with maximal bioavailability
- Process development, up scaling and GMP manufacturing of sterile implantable protein gel for bone regeneration
- Formulation optimization and GMP clinical supply in prefilled syringes of a phospholipid-based sustained released gel formulation.
- Development of analytical method for analysis of leachables and extractables
- Development of analytical methods, Preparative Separation and characterization of the synthesized material as reference standard

Key technical considerations

1. General

Prior to the beginning of any project, the client is requested to fill in a “Contract Review form”, in which information related to the project and its purpose of the project is required. Completion of the form to include all details will enable both parties to fully understand the needs and expectations and thus minimize misunderstandings. It is of utmost importance that when the needs concern development of a drug product for human use, information regarding the Active Pharmaceutical Ingredient (API), the indication and the route administration will be indicated.

Nextar’s experienced experts will be happy to provide consultation services when needed in order to help you do the minimum required work fits to the intended use.

2. Analytical services

2.1 Environmental Health and Safety

Prior to the commencement of the scope here within, a thorough review by Nextar of the Environmental, Health and Safety (EH&S) requirements for the API will be completed.

Client is responsible for maintaining and supplying current versions of the MSDS to Nextar, related to the Active Pharmaceutical Ingredient (API).

2.2 Method Transfer

Method Transfer is an onsite verification process in the receiving laboratory, which verifies that method performs in the receiving laboratory in a comparable manner to the originating laboratory. The Client needs to provide to Nextar the method validation or verification report. The following parameters will be performed at Nextar as the receiving laboratory:

- ✓ System suitability
- ✓ Accuracy
- ✓ Repeatability
- ✓ Linearity
- ✓ Quantitation Limit (If applicable)
- ✓ Stability of Standard and Sample Solution

2.3 Method Development

Sponsor may need to use a few methods along the product development. Those may include assay for quantification of the Active Pharmaceutical Ingredient (API), detection of impurities and degradation products, pH, osmolarity, dissolution of API (for capsules), Stability indicating methods, purity etc.

Please note that a method is defined as measurement of a specific element in a specific matrix/ hence a method developed for an API may not be suitable for the API mixed in a newly developed formula.

Development will cover, at least,

- ✓ sample preparation procedure,
- ✓ system suitability conditions, if applicable,
- ✓ accuracy and
- ✓ repeatability

It may also include other parameters such as sample stability, linearity and range.

2.3.1 Product Dissolution Assay by HPLC (Method Development)

For oral or semi solid dosage forms, Nextar will develop the assay required for testing dissolution of the product. The development will challenge the following parameters.

- ✓ Sink condition
- ✓ Specificity
- ✓ Selection of medium, Apparatus speed
- ✓ Accuracy
- ✓ Optimization of medium conc. & pH system suitability
- ✓ Repeatability

2.4 Bioanalytical Method Development and testing

Nextar will develop quantitative methods for API as active drugs, natural compounds and metabolites in biological fluids such as plasma, serum, urine, vitreous fluid and tissues. Bioanalytical assays are carried out routinely for small molecules, peptides and proteins.. Being recognized as GLP and GMP compliant laboratories

2.5 Method Validation- required from Phase IIB and on

Nextar will validate the test methods required to support the Project. The validation is "*the confirmation, by examination and the provision of objective evidence, that the particular requirements for a specific intended use are fulfilled" (VIM 2008).*

The following parameters may be validated:

- ✓ Quantitation Limit (if applicable)
- ✓ Detection Limit (if applicable)
- ✓ Accuracy
- ✓ Precision (Intermediate Precision)
- ✓ Linearity and range
- ✓ Specificity
- ✓ Sensitivity
- ✓ Robustness

The decision on the parameters that need to be validated depends on the purpose for which the method will be used (see definition above).

In addition solution Stability will be determined.

2.6 Stability indicating method (SIM)

The stability of a drug product must be tested. At a minimum one has to prove the stability during a toxicological or clinical trial. The stability data is also generated for the determination of drug shelf life (expiry date). It is expected that stability is tested using a method that is capable of distinguishing between the API and its degradation products. In order to prove that a method is Stability Indicating (SIM), we subject the drug product to forced degradation in different conditions (i.e. heat, acidity, U.V. light etc.). Than we need to prove the ability of the method (developed by Nextar or transferred to us) to differentiate the degradation products from the API.

Nextar will attempt to develop a method that may be used for testing Product Potency, Blend Uniformity and Content Uniformity for the API. If separate methods are required, incremental costs will be covered in a Change of Scope.

The following documents will be generated for each analytical method post development to support the CMC:

- ✓ Standard Operating Procedure (SOP)
- ✓ Validation or verification Protocols
- ✓ Verification or validation Report (data summary will be generated from developmental work)

3. Stability (Short and Long term)

Nextar shall design a stability program to monitor stability study:

Possible conditions:

-70°C±5° , -20°C±5° , 5°C±3°

25°C±2°/60%RH*±5%, 30°C±2°/65%RH*±5%, 40°C±2°/75%RH*±5%

*RH- relative Humidity

Samples will be tested (using at least one (1) SIM method, according to the desired purpose and developmental stage:

1. The period of the clinical study for preclinical and early clinical stages.
2. Long term studies for generation of data for registration drug product.
3. Accelerated conditions to enable prediction of long shelf life.

The analytical data used for the release of each lot manufactured at Nextar will be considered as initial (T=0) data if the stability study commences not more than 1 month after release testing.

4. Preformulation

Pre-formulation is the process in which different excipients are combined with the active pharmaceutical ingredient, are combined to produce a final medicinal product.
Pre-formulation studies may include, determination of physicochemical properties using in-silico tools (log P, log D, pKa), particle size distribution, zeta potential, drug-excipient compatibility and solubility.
Nextar will provide a protocol and report for Preformulation.

5. Formulation Development

Nextar`s formulation capabilities include a systematic strategy to develop the most appropriate formulation using potential approaches such as:

- ✓ Ionization of functional groups and salt formation
- ✓ Drug complexation with cyclodextrins
- ✓ Formation of stacking complexes to increase drug solubility
- ✓ Drug dissolution in water-miscible cosolvent systems

- ✓ Micellation by non-ionic-surfactants
- ✓ Self-emulsifying drug delivery systems
- ✓ Nano encapsulation in lipid-based drug delivery systems (liposomes, oil-in-water emulsions)
- ✓ Formulation of peptides and proteins using pharmaceutically acceptable solubilizing excipients
- ✓ Drug repositioning through new formulations or delivery systems for existing drugs

Nextar provides a protocol and report for Formulation Development.

6. Preparation of test articles for pre clinical study

Nextar prepares formulation of test articles and preparation for preclinical efficacy, pharmacokinetics and toxicology studies. The preparations may be carried out in the production plant under GMP conditions. However less expensive but still valid preparations may be done in a Biological hood which may save some cost but be limited in its quality.

7. Scale-Up and Clinical Trial Materials/Registration Manufacturing

Formulation development is usually done in a small scale. Production of a larger scale requires developmental work. Usually production of a batch, more than 2-3 folds, is considered scale up. Nextar recommends producing of a feasibility batch, the same size as planned for the GMP production for human use. A feasibility batch is required for the optimization of the process and to assure the consistency in the manufacturing. This batch will usually not be manufactured under cGMP and will not undergo a full QA review and approval.

Following the feasibility batch, when more information and experience is gathered, a GMP batch may be prepared for human use.

8. Microbiology

In order to avoid any contamination of Nextar's facility, Nextar will use a subcontractor laboratory to perform the following tests:

For non sterile products:

* Total aerobic microbial count and Total yeasts and molds count USP <61>, Pharmacopea Euopeanr (Ph.Eur) 2.6.12

* Test for specified micro organisms USP <62>, Ph.Eur 2.6.13 (depends on the administration route)

For sterile products:

* Sterility USP <71>, Ph. Eur 2.6.1

* Bacterial endotoxin USP <85>, Ph. Eur 2.6.14

Validation of microbial recovery from pharmacopoeia articles following USP<1227> guideline and USP Harmonized methods USP<61> and <62>). A harmonized specification based on USP<1111> will be followed to meet USP/EP/JP acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use. The validated methods will cover USP, EP and JP compendia for Microbiological Examination of Non-Sterile Products.

Each formulation and non proportional dose strength should be validated unless there is justification for matrixing. Each trial will be a different dilution targeted to establish adequate recovery.

9. Clinical Trial Material (CTM) and Placebo Manufacturing

Based on the experience gained from the scale up and prototype manufacturing, Nextar will manufacture the required clinical trial material under cGMP compliance according to ICH , European and USP and CFR guidelines. Time estimation for GMP production will be re-evaluated following feasibility batch. CTM is released, by Pharmacist in Charge, only when all test results are summarized and studied and according to the data gathered on the stability of the product.

10. Standard Assumptions

10.1 Provided that there are ongoing billable activities taking place (excluding stability) Nextar will provide project management support to monitor the progress of the project against established timelines and will provide client with updates.

10.2 It is assumed that the API and/or formulation do not absorb/adsorb to any metal, glass or other components used during the processing and analytical testing of the batch.

10.3 Nextar will receive and release the API for early phases cGMP manufacturing based on the following: (i) Identification testing; and (ii) the accompanying Certificate of Analysis (COA) from the API Vendor (Client qualified). In later stages more tests for characterization of the component will be carried out.

We will be happy to contribute to your drug development by facilitating your journey to clinical trials

For additional information:

Nextar Chempharma Solutions

Web site: www.nextar.co.il

E-mail: info@nextar.co.il

Address:

Einstein St. Building 13B, Weizmann Science Park, P.O.B 4147,

Ness Ziona 74140, Israel

Tel: 972-(0)-73-224-4444 **Fax:** 972-(0)-73-224-4445