New Drug Development, A QA Regulatory Overview

CDY-2020 is a NCE or New Chemical Entity (also referred to as a NME or New Molecular Entity) which is defined in the medical dictionary [1] as *"A chemically unique pharmaceutical that has not yet been marketed in the U.S. in any form."* The Code of Federal Regulations, 21 CFR Part 312 deals with Investigational New Drugs which includes New Chemical Entities. More specifically 21 CFR 312.23(a)(8) states "*Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations."*

As indicated by the Code of Federal Regulations, the FDA requires data that the NCE is reasonably safe for use in clinical studies. According to Karen McElvany [3], there are several options for fulfilling this FDA requirement, namely:

(1) provide a summary of existing data from past in vitro laboratory or animal studies on the compound

(2) provide a summary of data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the United States population

(3) perform new preclinical studies designed to provide sufficient evidence to support the safety of administering the investigational agent to humans

Since **CDY-2020** is a NCE, there are no previous clinical test data. At this stage, **CDY-2020** has only been demonstrated in in-vitro testing. Hence, from McElvany [3] further data including animal studies would be the next logical step in order to eventually support a Phase I clinical human study. This is in agreement with the FDA drug development information in [4] which states that

the following areas have to be addressed when submitting an Investigational New Drug or IND application:

- ***Animal Pharmacology and Toxicology Studies***
  Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
- ***Manufacturing Information***
  Information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and the drug product.
- ***Clinical Protocols and Investigator Information***
  Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks.

Therefore, based on these FDA expectations, it is recommended that **CDY-2020** move forward with the first step which will include discussions with the FDA on proposed animal studies. Per 21 CFR 312.82, very early "Pre-IND" meetings can be conducted in order to "*review and reach agreement on the design of animal studies needed to initiate human testing."* The proposal will be an in-vivo animal study which will include pharmacology and toxicity studies. As shown below in Figure 1, while the drug discovery process of **CDY-2020** was not regulated, during preclinical studies GLP or Good Laboratory Practices will be required. Thus, the **CDY-2020** preclinical animal study will be 21 CFR Part 58 compliant.

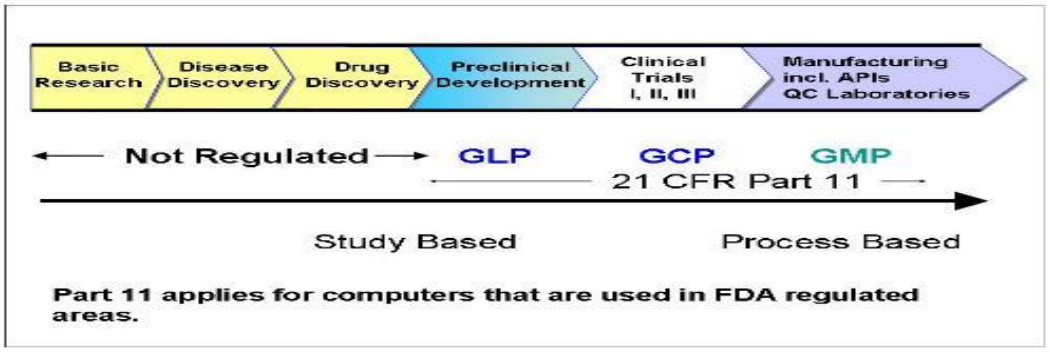

Figure 1. GLP vs. GCP, GMP and 21 CFFR Part 11
(from the LabCompliance tutorial at www.labcompliance.com/tutorial/glp/default.aspx.)

Based on the FDA's approval process [5], the **CDY-2020** animal pharmacology and toxicity studies will be performed in both rodents and non-rodents. The studies and dose durations will be based on the M3 International Conference on Harmonisation or ICH Guidance. Although **CDY-2020** is a NCE, it is not the only drug that is an inhibitor of renin-angiotensin system (RAS). Aliskiren [2] is a direct renin inhibitor that was approved by the FDA in 2007 and goes by the trade name Tekturna. As discussed by Novartis in [7], the Aliskiren preclinical toxicology studies included carcinogenic potential that was accessed in a two-year rat study, as well as genotoxicity and reproductive studies. Early Aliskiren studies also used marmosets that were helpful in establishing dose-response response relationships for human renin inhibitors. Given this existing data, **CDY-2020** will use Aliskiren as a comparative baseline when defining the preclinical protocols. Furthermore, the animal studies will be subject to 7 U.S.C. 54 U.S. Animal Welfare Act and any other applicable animal protection laws.

The second step per the FDA review presented in [4] will be to provide manufacturing information. This requires that we establish the stability of **CDY-2020** by means of Chemistry, Manufacturing and Control or CMC testing. CMC is needed since the IND application must contain *"Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.* [4]" Considering IND regulations require that **CDY-2020** remains within its specification for the life of the clinical trial, it will be characterized for its suitability to be made into capsules, tablets, injectables, or intravenous. During this process, we will be attempting to answer questions such as those proposed by Savello in [9]:

• Do I have a reliable synthetic route that is reproducible?

• Do I have a reliable, specific and sensitive analytical method?

• What are the physical chemical properties of the drug substance?

• Can it be readily formulated/delivered and maintain stability?

• How do I want to (need to) deliver the drug?

• What, if any, are the key properties of the drug that could confound clinical results?

• Can I produce a compliant and convincing CMC package?

The third step will commence with another Pre-IND meeting with the FDA per 21 CFR 312.82 which further states: "*The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, and the best approach for presentation and formatting of data in the IND."* Following this meeting with the FDA, the IND will be submitted using the following forms:

- Form 1571 which is the Investigational New Drug Application.
- Form 1572 which is the Statement of the Investigator that provides information about their qualifications to participate in the studies.
- Form 3674 which is the Certification of Compliance where the sponsor states all applicable requirements have been met. Title VIII of FDAAA Section 402(j) to the Public Health Service Act (42 USC § 282(j)) requires that, at the time of submission of an application under section 505 of the FDCA, including an Investigational New Drug application, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met.

CDY-2020 will be submitted as a Commercial IND using the following FDA Guidance Documents:

- Guidance for Industry: CGMP's for Phase 1 Investigational
- Guidance for Industry: Exploratory IND Studies
- Guidance for Industry : Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs Including Well Characterized, Therapeutic, Biotechnology-Derived Products
- Guidance for Industry : Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations

- Guidance for Industry : Drug Master Files
- Guidance for Industry: Immunotoxicology Evaluation of Investigational New Drugs

Although Phase 1 trials are not typically blinded, using the recent ongoing the clinical trial of SPP676 (a new renin inhibitor) as a precedent [10], the Phase 1 trial of **CDY-2020** will be a placebo controlled double blind study in forty healthy male volunteers for six months. The trial will evaluate the safety and tolerability using single and then multiple oral doses. As shown earlier in Figure 1, the Phase 1 trial will use Good Clinical Practices or GCP. We will make commitments to obtain informed consent per 21 CFR Part 50 Subpart B from the research subjects, to obtain review of the study by an Institutional Review Board or IRB per 21 CFR Part 56, and to adhere to all Investigational New Drug regulations per 21 CFR Part 312. After submitting the IND, we will wait 30 calendar days before initiating Phase I.

Finally, our IND post approval obligations will consist of the following:

- Selecting qualified investigators and monitors
- Providing necessary information to investigators
- Monitoring the research
- Controlling the investigational product
- Reporting significant adverse events to FDA, IRB, and investigators
- Maintaining the IND
- Maintaining and Retaining Accurate Records

References:

[1] The Free Dictionary, **http://medical-dictionary.thefreedictionary.com/New+Molecular+Entity**

[2] U.S. National Library of Medicine - The World's Largest Medical Library, **http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000389/**

[3] Karen McElvany, "FDA Requirements for Preclinical Studies", University of North Carolina School of Medicine, Chapel Hill, N.C., US

[4] FDA.gov, "Drug Approval Process", **http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176522.htm**

[5] FDA.gov, "Drug Development and Review Definitions",

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176522.htm

[6] Mark Mathieu, "New Drug Development: A Regulatory Overview", Parexel International Corporation, 2005

[7] Novartis Pharmaceuticals, **http://www.pharma.us.novartis.com/product/pi/pdf/tekturna.pdf**

[8] Wikipedia, **http://en.wikipedia.org/wiki/Drug_development**

[9] David R. Savello, Chemistry, Manufacturing, and Controls of Drug Candidates for Dummies, SVP Drug Development, XenoPort, Inc.

[10] MedScape Today, **http://www.medscape.com/viewarticle/567233_3**