

# CFR Part 11 Compliance

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*The Cognizant Approach*



**Cognizant  
Technology  
Solutions**

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## Introduction

The manufacture of pharmaceuticals is an enormous and highly profitable industry. Since 1990, pharmaceutical industry is clocking a healthy EPS growth rate of 15 % as compared to S&P 500's 7%. Despite the huge profits to be made, the drug industry is highly regulated and competitive with soaring R&D costs (estimated at 17 % of sales), and business critical regulatory compliance costs.

The drug industry's response to these pressures have been manifold with focus on operational efficiency, cost reductions, aggressive marketing strategies and to a significant extent using the technological advances in Information Technology.

Today in a pharmaceutical company, many key decisions and actions are being taken through electronic interfaces, with manufacturing as well as regulatory records like batch production records, certificates of analysis, new drug development data being generated and stored electronically.

The FDA rule relating to use of Electronic Records and Electronic signatures (21 CFR Part 11) is an effort by the FDA to set minimum compliance guidelines for computerized systems operating in the pharmaceutical industry. 21 CFR Part 11 ruling, which is substantive in nature, extends scope of FDA inspections to include IT departments also thus making many organizations vulnerable to non-compliance.

Cognizant addresses CFR compliance regulations from different perspectives and provides solutions and services for compliance assessment, testing, remediation, deployment and maintenance thus covering all the aspects of software life cycle. Cognizant has now assembled the knowledge, methodology, peoples and tools to assist pharmaceutical companies in achieving CFR compliance quickly, with the least disruption, and at the lowest cost.

## 21 CFR Part 11- an overview

21 CFR Part 11 establishes requirements to ensure that electronic records and electronic signatures are trustworthy, reliable and generally equivalent substitutes for paper records and traditional handwritten signatures. Electronic records and electronic signatures may be used to meet record and signature requirements of 21 CFR Parts 210 and 211 when Part 11 requirements are met.

As defined by the FDA, "Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system."

The electronic record also includes output from instrumentation (digital signals combined with defined parameters for manipulating signals), software code, etc. These regulations apply to records required by predicate rule, which is a previously published regulation such as Good Laboratory Practice (GLP), and Current Good Manufacturing Practice (CGMP).

Similarly, according to the FDA, "Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature."

Signatures required by predicate rules when executed electronically fall under Part 11 compliance. Part 11 also covers non-required signatures if they are executed against required electronic records.

## **21 CFR Part 11 - an assessment**

Compliance with regulatory requirements is a business-critical need that can create significant costs. Management would like to reduce compliance costs without increasing the risk of compliance failure, whilst also eliminating compliance failures without incurring incremental costs.

21 CFR Part 11 brings significant benefits to Pharmaceutical companies by

- Legalizing the electronic record keeping in GMP, GLP environment.
- Acceptability of electronic submissions in areas of new drug applications and updates
- Permitting the introduction of new technology
- Preventing fraudulent changes being made to electronic records.
- Significant cost reduction through standardization
- Simplified exchange between industry players
- Increased use of electronic transactions and automation
- Ability to leverage e-business technologies
- Improved public perceptions and enhanced industry credibility

But at the same time it enforces certain requirements for which the computer systems in a pharmaceutical company are not prepared. Though there have been efforts from the software vendors to launch CFR compliant systems and software, the existing systems (legacy systems) are not compliant. Also newer systems in general are not accompanied by statements of suitability, or compliance with established requirements but rather by disclaimers as to their fitness of use.

FDA also takes a realistic approach towards the problems faced by industry. It recognizes that it will take time for existing systems to attain full compliance with 21 CFR Part 11. While dealing with non-compliance situations FDA focuses on following points:

- Impact on product quality and data integrity
- Adequacy and timeliness of planned corrective measures
- Compliance history of a company especially with respect to data integrity.

Another issue of grave importance is lack of standard interpretation. There are several gray areas where the interpretations differ among the individual companies. Though FDA is trying hard to clear the misunderstandings, the implementation is surely going to get affected. Some of these issues are:

- Identifying the electronic records covered under 21 CFR Part 11 ruling
- Maintaining audit trails

## 21 CFR Part 11 Compliance- The Cognizant Approach

- Resolving Data integrity
- Identifying users
- Enabling secure transactions
- Incorporating checks for CFR compliance
- Devising Change control procedures
- Identifying software configuration issues
- Resolving biometrics v/ non- biometrics signature conflicts

Whether open or closed, new or old CFR regulations apply to all the systems and companies should chart out a detailed implementation plan that suits their business goals.

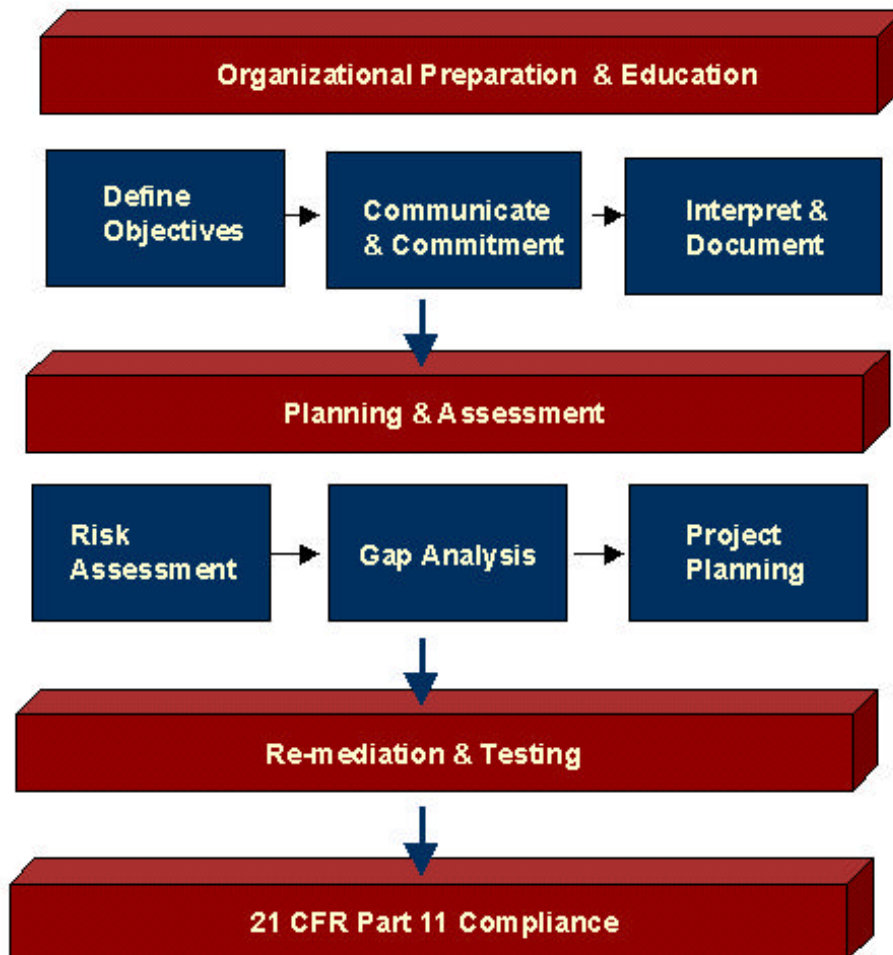
Cognizant has several thousand-person years of software development experience for Fortune 1000 companies. While being assessed as SEI-CMM level 5, Cognizant focuses not just on coding solutions but cautiously designs and monitors all the aspects of software development including requirements gathering, gap analysis, testing, change control procedures and configuration management. All the deliverables move through QA/QC assembly line for validations and checks. In addition cognizant's clients benefit from cost-effective solutions, 24x7 work model, and assured reduced time-to-market.

With its experience in providing CFR Part 11 solutions, Cognizant can play a facilitating role in

- Conducting Gap analysis in conjunction with client's validation resources
- Establishing user identity, user accountability and procedures in various SOPs for personnel developing, maintaining administering or using a system.
- Validation testing for systems to ensure accuracy, reliability and operational consistency
- Defining enterprise wide security policies
- Designing audit trails and archiving mechanisms
- Establishing and implementing document control procedures

## Cognizant CFR Part 11 Methodology

Cognizant has developed a phased methodology that encompasses the entire CFR Part 11 compliance process, from preliminary planning and education through assessment to re-mediation and testing. Our CFR methodology organizes the compliance process into three stages: 1) Organizational Preparation and Education, 2) Planning and Assessment, and 3) Re-mediation and Testing. We offer CFR services corresponding to each stage of the process.



### Organizational Preparation and Education

To begin an effective CFR Part 11 compliance effort, the organization must understand CFR Part 11, create CFR Part 11 awareness within the organization, and educate its staff and other stakeholders about the specific regulations and requirements. As a very first step towards the CFR Part 11 compliance it is imperative for an organization to:

- Define a set of objectives for achieving compliance
- Communicate the implications of Part 11 for people involved and ensure the commitment to resolve non-compliance
- Define a common interpretation of Part 11 based on individual company needs

These basic steps create an awareness of CFR Part 11 compliance within an organization and prepare the organization for changes expected due to CFR Part 11.

### **Define objective**

Cognizant's approach is not only to help organizations in defining objectives for compliance project but at the same time evolve a universally accepted plan to achieve the objectives. Cognizant will facilitate stakeholders in:

- Understanding the regulations,
- Understanding the resource and budget requirements
- Matching roles with responsibilities defined under the rule
- Defining action plans for non-compliance
- Envisioning tools for compliance assessments
- Identifying business benefits

### **Communicate and ensure commitment**

Cognizant methodology believes in creating organization wide awareness about CFR Part 11 through selective and targeted education and training. By working closely with Client's analysts, Cognizant associates identify the positive impacts of CFR Part 11 compliance on the business (for e.g. operational efficiencies) and work towards ensuring organizational commitment to that extent. Cognizant will focus on deliverables that address:

- Impact on new and existing systems and outstanding issues with CFR Part 11 compliance
- Need for defining QA/QC procedures for compliance
- Readiness of IT department and software vendors for compliance
- Outline of the proposed approach to be followed

### **Interpret and Document**

There are many interpretations of Part 11 compliance available with software vendors, consultants, IT managers, business managers all interpreting it differently. Also, the compliance requirements for an organization may totally differ from that of other. Cognizant as part of an expert group involving people with GXP experience can help in bringing consensus on how the rule be interpreted for a particular compliance project. The standard interpretation will be documented, and communicated across the organization to ensure a common understanding.

Cognizant deliverable in this area focuses on areas like:

- Validation
- Security
- Training
- Checks and controls
- Audit trails
- Archiving and retrieval
- Documentation controls

## **Planning and Assessment**

In this phase, Cognizant looks at the specific systems and processes that must be brought into CFR Part 11 compliance covering all the aspects of system including application, operating system, network, hardware and all associated services. Cognizant continuously updates its capabilities across compliance service spectrum with iterative prototypes involving unique combination of business and technology needs. Our methodology for planning and assessment assists the organization in conducting:

- Risk assessment exercise to identify IT systems that are most vulnerable to non compliance
- Functionality / gap analysis to determine the level of compliance for key business areas and IT infrastructure
- Project planning based on the gap analysis detailing the extent of validation required.

## **Risk Assessment**

Current GXP requirements describe maintaining a list of current systems. This list can act as starting point for risk assessment exercise. The assessment process consists of a review of the existing systems to ensure that these systems create, capture or maintain data in electronic form. The systems requiring Part 11 gap analysis are identified based on a set of checklist. Cognizant follows its rigid QA review process for the exercise and mandates that the competent QA authority reviews the exercise.

Risk assessment exercise takes input from existing procedures like:

- SOPs or user operating procedures
- Software audits performed for assessing software vendor's standards and practices
- Reviews performed for software requirements.

## **Gap analysis**

Cognizant adopts industry wide standards to perform the gap analysis for CFR Part 11 compliance in the systems identified above. The standards have been given a Cognizant touch to fit it seamlessly with Cognizant's software quality processes. With our experience in e-business and new technology projects, we have been able to high light the common issues with electronic

record keeping, security, role based authentication to name a few. Thus, the Gap analysis deliverables are useful not only for CFR Part 11 project planning but for re-engineering, maintenance and migration project planning also.

Some of the highlights of the Gap analysis process are:

- Procedures and control for closed systems
- Procedures and control for open systems
- Electronic signatures
- Controls for identification and password entry
- Security audits which address administrative procedures, physical safeguards, security mechanisms and security services

### **Project Planning**

The process creates an estimate based on the gap between your existing environment and CFR Part 11 standards. Once the gaps are identified, we prioritize the applications and business processes, which are to be made compliant, based on their functionality and business criticality. Deliverables in this stage include:

- List of systems requiring compliance
- Prioritization of systems based on issues like data integrity, extent of compliance etc.
- Detailed action plan for each of the identified system
- Resource and project plan for re-mediation

### **Re-mediation and Testing**

This is the final stage of our CFR Part 11 compliance methodology. Based on the assessment and gap analysis reports, requirements for code changes and or testing are identified and detailed implementation of remediation efforts is carried out as per agreed upon project plan.

When planning re-mediation, Cognizant consider numerous factors, including:

- Speed at which the company can re-mediate systems
- Time available to re-mediate all the affected systems
- Availability of the application and systems experts who helped design the systems to assist in the re-mediation process
- Change management issues
- Level of risk that the organization is willing to assume
- Preparation of backup and contingency measures to ensure continued reliable service to customers both during and after the CFR Part11 compliance process
- On-going monitoring process

## **Benefits of Cognizant CFR Part 11 methodology**

The Cognizant approach to CFR Part 11 compliance is both comprehensive and flexible, enabling any organization to achieve full compliance in the shortest possible time and with the least disruption. Gap analysis ensures that the effort focuses only on what specifically needs to be done, while at the same time providing critical decision support information for re-engineering and maintenance projects.

For e.g., the laboratory information systems of today are transforming in to SDMS (scientific data management systems) that can capture disparate data from multiple sources—laboratory instruments, graphical interfaces, documents, and more.

Cognizant as part of its re-mediation plan discussed above can propose developing solutions with open electronic formats (like HTML, XML) and which can automate collection, storage and sharing of scientific data to a centralized data base at the same time creating online laboratory reports. Our solutions will address features like centralized data, single point of entry, single sign-on, e-security by using technologies as Digital certificates, EAI, LDAP, leveraging our wide experience in Data warehousing, EAI, e-Security and newer technology projects (Internet technologies). Our methodology can thus help organizations to fit CFR Part 11 compliance needs in their overall IT maintenance and development plans.

The payback for the organization comes in a number of ways:

- Faster, easier compliance through a robust, tool-based approach
- Higher quality compliance
- Cost-effectiveness
- Opportunities to improve/enhance systems and processes
- Ability to leverage CFR Part 11 for re-engineering and e-Business initiatives

Supplementary benefits include:

- Improvement in GXP processes
- Better understanding for data integrity
- Better co-ordination between IT and Business experts

## **21 CFR Part 11 - a case study**

### **Client Situation**

Food and Drug Administration, USA have announced a set of regulations (CFR-11) to allow maintenance electronic records and electronic signatures instead of hardcopies in drug manufacturing processes. The client has a number of processes with electronic recording of the process inputs, outputs and status details. Clients have taken an integrated approach to track CFR Part 11 compliance of its applications.

### **Cognizant's Solution**

In order to monitor the CFR Part 11 compliance enabling process, Cognizant developed a web-based tracking system. This would enable the following:

- Fill the Assessment Worksheet - The purpose of the worksheet is to specify the criteria under which electronic records, electronic signatures, and handwritten signatures executed to electronic records are considered equivalent to paper records and handwritten signatures executed on paper in accordance with 21 CFR Part 11 (the Regulation).
- Evaluate a computerized system versus the established requirements
- Document the evaluation of the computerized system
- Monitor the status of CFR Part 11 compliance of all processes.

The system, currently in production, provides a consolidated information and an application-wise breakup of the same. It also acts as a centralized medium to collect information on items missing in the inventory.

Cognizant delivered solutions using a seamless onsite and offshore project management model. A dedicated link between the client & Cognizant Off-shore Center (Calcutta) was established in initial stages of this project to facilitate this methodology.

### **Client Benefits**

- Economic pricing due to onshore-offshore model
- Quick staff augmentation onsite
- Quick and anytime access to information
- Better informed decision making
- Access to real time consumer information
- Information access from any point of operation (geographically spread)

### **Technology**

Keeping in view the operational requirements on multiple platforms like MAC, Windows 95, Windows NT & Unix, Cognizant employed a Microsoft IIS 4.0 web-server, Active Server Pages and Java Script based front end development, Crystal Reports 6.0 as the report writer and a ORACLE 7.3.4 as back end.

## **21 CFR Part 11 – a Project Profile**

### **Profile**

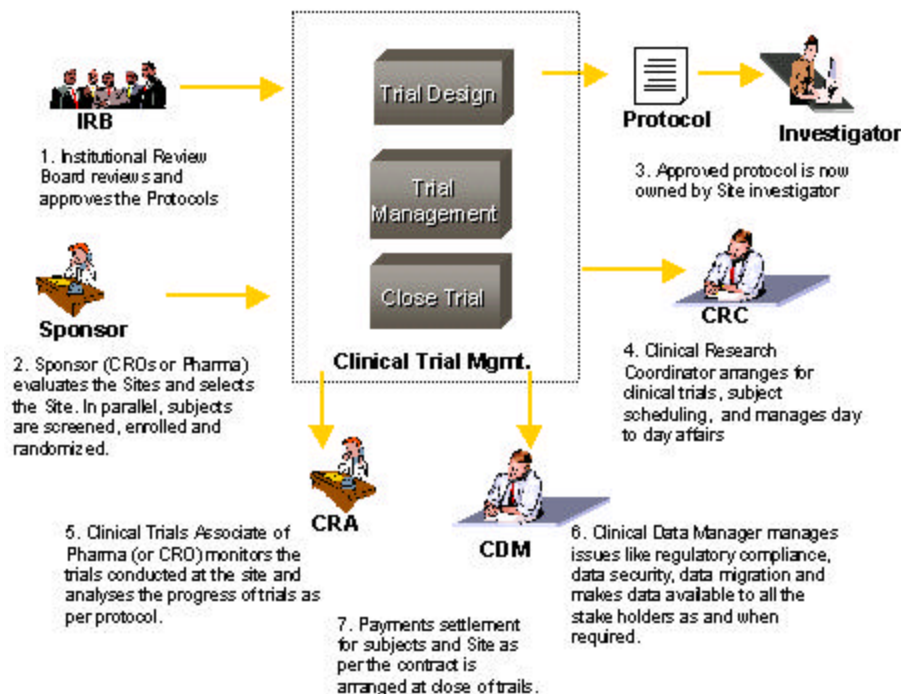
The Client, a leader in web-based clinical trial data collection and management software and service, accelerates the delivery of new and beneficial drugs and medical devices to market and helps clinical trial sponsors in eliminating the need to transcribe and process traditional paper data forms.

Client's solutions include:

- A web based clinical trial environment serving the needs of site coordinators, physician investigators, monitors, clinical data managers, project managers, safety and medical monitors, and clinical investigators.
- An outsourced ASP service that provides the benefits of clinical trials environment without requiring in-house infrastructure investments and the learning curve associated with the adoption of new technologies.

## Situation

The current process of clinical trial involves many transcriptions and relies heavily on manual inspection and data checking late in the process. Management decisions are based on incomplete, inaccurate information collected at considerable labor cost (Averaging \$100 per query).



**A Representative Clinical Trial Process**

By moving data collection upstream, augmented with up-front automated data cleaning, sponsors can substantially reduce costs and increase capacity. In addition to this, decisions are made on real-time information, enabling Pharmaceutical companies and/or Contract Research Organizations (CROs) to run the trial efficiently.

Client framework adopts a three-stage methodology for planning, execution and management of clinical trials.

First step is Trial Design phase involving study preparation, eCRF (Clinical Record Form) design and training. As per the process, client gets the approved protocol from sponsor and customizes its solution framework to initiate the Site for clinical trial.

The site should go through a detailed QA testing phase to validate

- Compliance with regulations like 21CFR part 11, Good Clinical Practice (GCP), FDA guidance on computerized systems used in Clinical Trials
- Conformance with requirements as defined in protocol

Trial Management occurs as the second step, which involves managing the clinical trials framework. It is the phase in which the various actors interact with the system.

Close Trial indicates the completion of trails and involves Database archiving and delivery.

## **Solutions**

Client, driven by competitive pressures, initiates a product release each quarter with patch releases almost every month. Till recently, Client's QA department was performing manual regression tests using a regression test suite comprising over 4000 test units. This was an expensive but mandatory activity to ensure that the releases were smooth and do not impact trials that are already being supported by the product. Cognizant is helping in automating their entire Regression test suite using 'WinRunner', a test automation tool. Cognizant has implemented several work-arounds to overcome WinRunner limitations to ensure near 100% automation.

As major releases happen every quarter, the window available for automation between any two-release cycles was only 11 weeks. Cognizant stepped in and suggested the onsite/offshore model for test scripts automation, as a part of which cognizant has created a complete test environment at its Chennai facility with 30 resources.

Cognizant delivers automated/tested test scripts on a weekly basis for client to verify and incorporate the new scripts into their QA environment, thus making the acceptance phase much easier.

Using its CMM level 5 assessed QA processes and enhancing it for 21 CFR part 11 and GCP requirements, Cognizant is helping its client in delivering a clinical trials solution which is complete, accurate, reliable and consistent in its intended performance. Cognizant is actively involved in every phase of clinical trials management and supports activities such as:

- Customizations for Trial Design stage
- Trace ability of requirements for GCP validations during all the three stages
- Creating data extracts for Sponsors in custom defined formats during Trial Management and Close Trial stage

Cognizant has also developed a Web based workflow tool for effective Project Management. This tool, provides features like:

- Resource planning and scheduling to aid in efficient customization and verification
- Defects tracking
- Metrics generation for effective control

The relationship is now extending to provide technical solutions in the areas of product customizations to suit specific trial requirements.

## **Benefits**

Benefits to client include:

- Use of automated tools to ensure quick and reliable test for each launch
- Unique onsite-offshore model for cost effective ness and smooth execution
- Proven methodologies to enable iterative development
- Web based project management tools for effective control
- Improved focus on strategic priorities by outsourcing

On the other hand, Cognizant by virtue of this project has also gained knowledge in regulatory compliance guidelines such as Good Clinical Processes (GCP), 21 CFR Part 11 compliance.

## About Cognizant

Cognizant is a leading provider of e-business solutions and application management services, helping clients to manage rapid changes in technology and to achieve business objectives. We deliver cost-effective solutions to Fortune 500 & Blue Chip companies worldwide, and this year were named the top IT services provider in Forbes Magazine's Best Small Companies list, and in BusinessWeek's 100 Hot Growth Companies.

Cognizant's competitive advantage and the source of great value to our customers comes from our unique business model which offers:

- **High Quality** - Cognizant is SEI/CMM Level 5 across all its development centers in India, one of only a small number of IT services providers worldwide to have achieved this remarkable distinction. To ensure the highest possible quality of software development and maintenance, we have devised a Quality Management Process that emphasizes problem prevention rather than problem correction. This Quality Management Process integrates our quality approach throughout the software development life cycle, thereby ensuring that quality is built in as development progresses. Additionally, our large project expertise is reflected in strong methodology and the use of proprietary tools. We streamline project management functions with eCockpit, a project management tool that provides a graphic representation of project-related data such as productivity and effort, and personal metrics such as targets individual progress and cash flow.
- **Fast Turnaround** – In a typical customer engagement, 20 percent to 30 percent of Cognizant team members work at the customer site and 70 percent to 80 percent of the team members are located at one of our nine offshore development centers in India. The on-site team interacts daily with the customer to define requirements, review prototypes and manage scope changes. This business model allows us to serve customers 24 x 7. When U.S. workers are settling in for the night, programmers in India are just starting their day. We also have an extensive communications network that provides 24x7 high bandwidth communications links between the India-based development teams and every client. This provides dedicated high-speed support to help meet tight deadlines and support mission critical applications.
- **Cost Effectiveness** – Our on-site/offshore methodology ensures quality execution at a low cost
- **Access to Hard-To-Find Skills** - Our expertise extends across a wide range of technologies encompassing ebusiness, data warehousing and customer relationship management, as well as legacy and client-server applications. Our industry experience extends to providing solutions to several information-intensive industries such as healthcare, insurance, banking, financial services, and retail and information services.

### Contacts

To learn more about Cognizant's Pharma service offerings, please get in touch with:

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