cGMP Informatics

IT Infrastructure Design for 21st Century Pharmaceutical Quality Control and Quality Assurance Operations

VelQuest®

The GMP Electronic Notebook People®

Table of Contents

Introduction 03

A Three Tiered cGMP Informatics Architecture 03

System Responsibilities in an Optimized Three Tiered cGMP Informatics Architecture .. 04

Workflow Diagram of an Optimized 3 Tiered cGMP Informatics Architecture 05

LIMS and GMP Electronic Notebook Boundaries 05

LIMS and GMP Electronic Notebook Comparison Table 06

Workflow Diagram of a QC/QA Laboratory 07

GMP Electronic Notebook System architecture diagram 08

Benefits of a GMP Electronic Notebook System in a cGMP IT infrastructure 08

Conclusion 09

cGMP Informatics: IT Infrastructure for 21st Century Pharmaceutical Quality Control and Quality Assurance Operations

Introduction

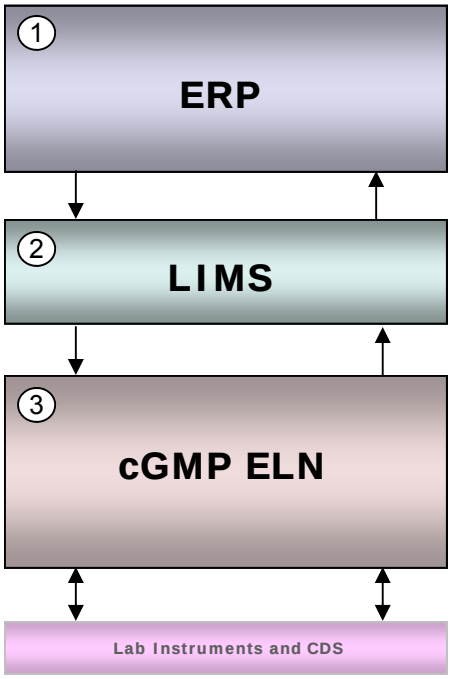
The pharmaceutical industry is in a state of transformation, driven by two basic challenges: 1) cost reductions as a result of margin erosion pressures, and 2) improvements in compliance documentation and reporting. Both challenges are being addressed by several initiatives under topics including lean manufacturing, right-first-time, six-sigma and operational excellence programs. The foundation of all of these programs is the need to eliminate the non-value added tasks associated with the workforce and workflow at all levels within the manufacturing environment.

At a recent industry conference (1), senior quality operations managers emphasized the importance of the laboratory execution or "work-layer". While the planning and administration layers of a typical pharmaceutical company have been automated with ERP and LIMS respectively, the laboratory execution layer has been either lumped in with LIMS or been left behind altogether. A relatively new technology to automate this laboratory work layer is the Electronic Laboratory Notebook. Within the GMP regulated areas such as QC and Manufacturing, a GMP Electronic Notebook System ensures that only trained analysts/operators can execute only current SOPs and test methods using only approved instruments and supplies. Automating these processes with an electronic platform eliminates the paper-based processes that contribute to operational costs and compliance risks.

This white paper will outline a three tiered IT architecture comprised of an upper layer ERP platform, a middle layer LIMS for lab administration, and a lower layer GMP Electronic Notebook for lab execution. This architecture enables a paperless cGMP Informatics structure that delivers productivity, cost and compliance benefits for 21st century pharmaceutical manufacturing.

A Three Tiered cGMP Informatics Architecture

In a large pharmaceutical production supply chain environment, higher-order IT systems such as Enterprise Resource Planning (e.g. SAP) are considered the global integration hub for managing all operational resources. The ERP system issues work orders for production, which in turn triggers LIMS to assign work and capture results for quality testing (raw materials, in process, stability, and finished product). A QA review and approval process results in lot release.



Traditionally, the laboratory execution workflow is documented on paper, in the form of lab notebooks, forms, data sheets and packets, instrument data binders and supplies/calibration log books. These paper-based processes are the most likely source of confusion and documentation errors. Catching these errors with peer and management review processes, while done to assure completeness and compliance, results in lengthy cycle times. These inefficient processes are thus on the critical-path for improvements.

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These manual processes have been identified as the efficiency bottleneck and are the non-value added and often error-prone contributions to the data capture and cataloging process. It is precisely here that the GMP Electronic Notebook layer adds significant value. It eliminates the paper issues and forces analyst/operator compliance consistent with validated GMP requirements at *each method step.*

The workflow tasks associated with each layer of an optimized three-tiered GMP Informatics IT architecture is outlined below:

System Responsibilities in an Optimized 3 Tiered cGMP Informatics Architecture

Functional Area/Tasks	ERP	LIMS	ELN
Production Process Order is Released	√		
Raw Materials Enter Facility	√		
Production Process	√		
Quality Testing Requirements Planned	√		
Testing Scheduled for Batch Release or Stability		√	
Receive and Log Samples for Testing		√	
Testing Specifications identified		√	
Samples and Work List deployed in Labs		√	
Methods executed by trained Analysts/Chemists			√
All Reagents, Standards Prepared and “pedigree” Logged			√
Instrument Data Captured and Linked to Method, Person, and Supplies			√
Instrument Data Parsed, Reported, and Linked to Method			√
Calculations Performed and Results created			√
All data Reviewed by Supervisor			√
All Rework performed			√
Final Review within Lab Operations			√
Trending Reports with Instruments, Analysts, Methods			√
Results Reporting and checking against Specifications		√	
Batch Results posted for formal evaluation		√	
Final Batch Results posted to ERP for Final Disposition	√		
Production Reporting	√		

In this workflow, the lab administration layer tasks are limited to key management level operations (specifications, lot and sample input and reporting), thus eliminating the “customization” and costs required to integrate the LIMS with lab instruments, lab procedures and the important metadata pedigree needed for compliance. The “work layer” is then centralized within the GMP Electronic Notebook layer and fully integrates with ALL lab instruments, methods, supplies and analysts.

This process expedites bi-directional data flow between laboratory and manufacturing operations, while ensuring regulatory compliance and integrated data capture and reporting on a global basis. System responsibilities from table 1 are depicted as a workflow diagram below (figure 1).

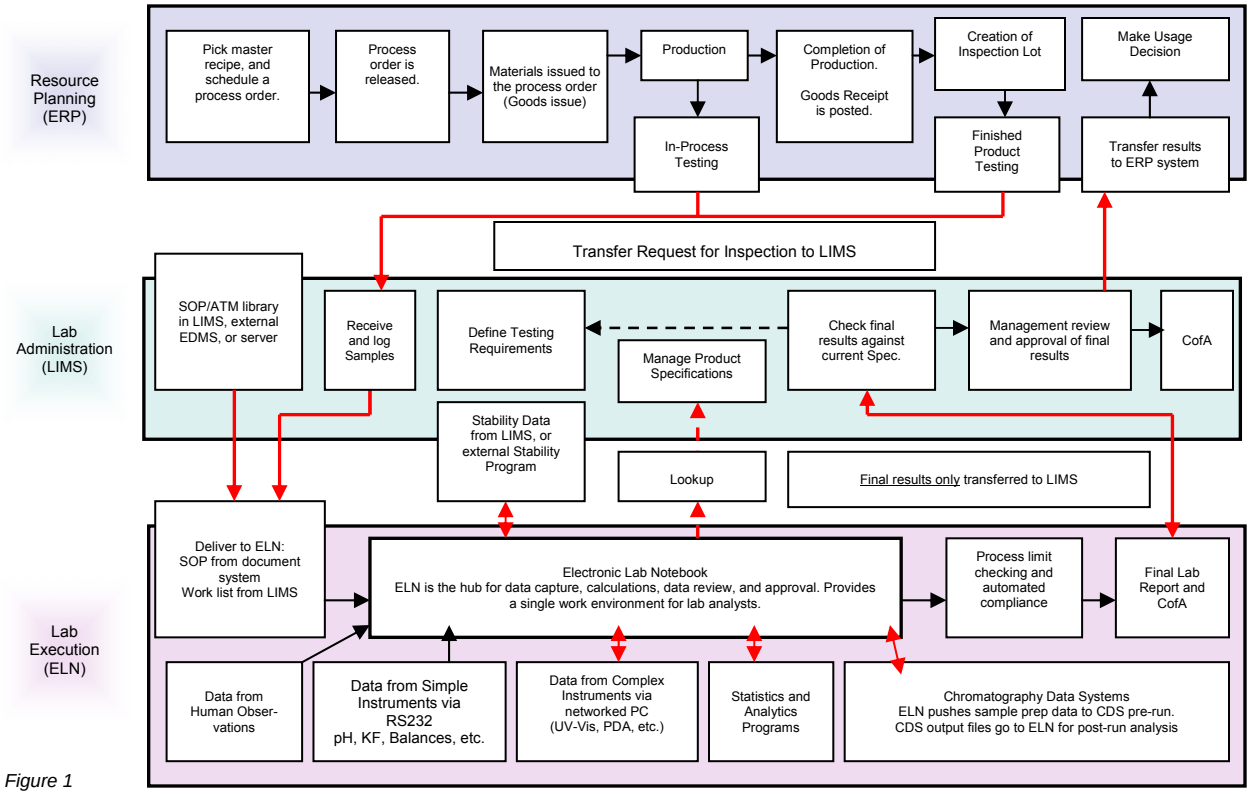

Figure 1

Three-tiered cGMP Informatics IT Infrastructure including ERP, LIMS and Lab Execution (GMP ELN) where all methods, instruments and analyst/ operator procedures are executed with automated data and metadata capture and transfer to other IT layers.

LIMS and GMP Electronic Notebook Boundaries

Organizations that have deployed a LIMS have generally used it as an electronic file cabinet to fulfill administrative functions, such as sample tracking and results management. A typical LIMS deployment rarely delivers compelling productivity gains in optimizing laboratory processes. What LIMS excels at is the distribution of critical-path quality results throughout the global QC/QA enterprise.

However, a key compliance issue is the primary data *and* associated metadata produced by the execution of actual test methods and SOP's by analysts and operators (see figures 2 and 3). In traditional LIMS, data such as instrument calibration records and analyst observations are rarely automatically captured *during* method execution. The importance of this data and metadata cannot be understated, as it represents critical information for the investigation of any failed test that is required for lot or batch release, or a regulatory agency site inspection.

Figure 2

The GMP Electronic Notebook system presents a digital version of a standard test method (STM) to an analyst with automatic capture of data (and metadata) seen in the lower portion of the window. This process eliminates the transcription errors and calculations associated with paper-based notebooks, and is extremely easy to use for the chemist/analyst.

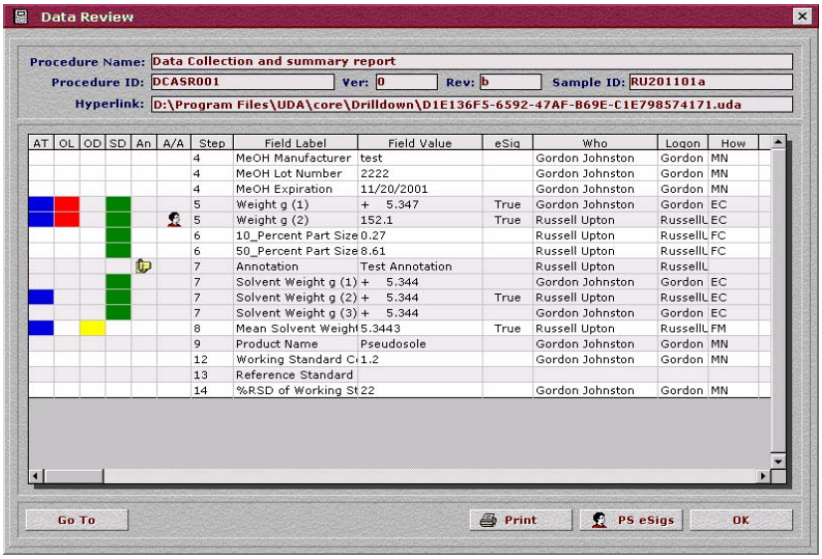

Figure 3

After a method is completed, all data and metadata is presented to reviewers in a dashboard with visual compliance flags.

Flags can alert reviewers to primary data and materials expiration requirements, instrument calibration dates, audit trails, annotations, e-signatures and direct, single mouse click "drill-down" links to the raw data sources.

Today, the LIMS initiatives in the life science industry are focused on launching work (sample administration), storing specifications and final results, and generating reports. Typically, lab or work area results are entered via result entry forms (usually manually) and accompanied by an instrument output report. LIMS are traditionally product-centric at both the corporate and local levels. In comparison, the GMP Electronic Notebook is method-centric. Since nearly every process in a GMP facility is governed by a method, the analyst can use the GMP ELN for all instruments (CDS, balances, pH meters, particle size analyzers, dissolution testers, spectrophotometers etc.) and reagents, standards and supplies (see figure 4). The key business level boundaries are outlined below:

	GMP Electronic Notebook Systems	**LIMS**
Primary User Focus	Lab Analyst, Plant Operator	Lab Manager and Director
Primary Focus	Execution of Standard Test Methods (STMs), Standard Operating Procedures (SOPs)	Storage and reporting of product specifications and final results
Business Drivers	Compliance & Productivity at bench level	Final Product Result Management
Design Approach	Highly Structured Method Centric	Structured; Product and Result centric
Electronic Data Capture and Integration in lab infrastructure	Primary data centric; dynamic real-time capture from observations, all instruments, and other data systems (CDS, ERP, LIMS)	Result data centric; Custom integration with limited instruments and other data systems (CDS, ERP), Forms based.
Searching and Reporting	Audits and Investigations, in-process data review. Performance assessment reports for methods, instruments, and analysts.	Specification based reports, final summary results reporting, certificates of analysis.
Validation Effort	Standard templates, COTS, minimal revalidation with configuration changes. Methods evolve.	Frequently requires customized validation scripts.
Resource Requirements	Creation and configuration of entire lab execution layer is done in standard product.	Programming experience is usually required for customization and interfacing
Vendors	VelQuest, Waters, Labtronics	LabWare, Thermo, ABI, LabVantage, StarLIMS

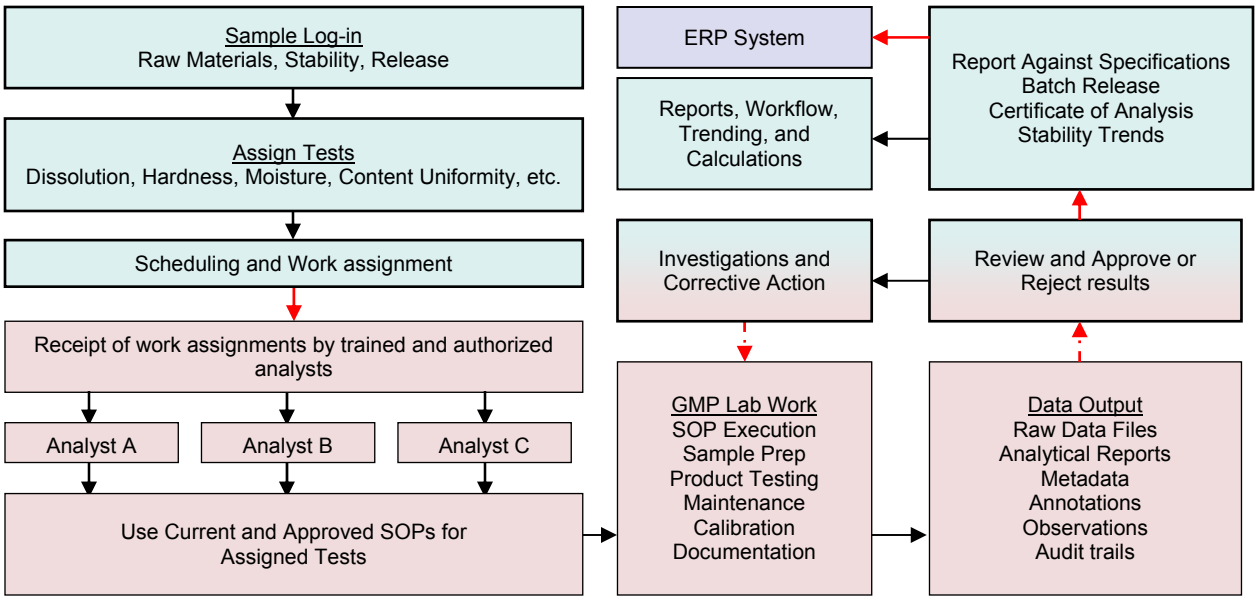

Figure 4

The compliant paperless automation elements in the lower portion of this figure are provided by a GMP Electronic Notebook platform. Traditional LIMS functionality is outlined in the top portion (blue shading) of the figure. In a traditional LIMS, the actual method execution and data collection tasks are processed via paper forms with non-value added transcription/translation that must be checked and verified before manual entry into the LIMS. Through integration of the GMP ELN layer and LIMS functions, a paperless and automated GMP informatics platform is realized.

Validation

As a final point of comparison, the validation approach to GMP Electronic Notebook solutions is very different than traditional validation approaches used in LIMS and research-based ELNs. Traditional LIMS solutions that are customized to do lab execution tasks require hard coding features that can trigger significant system-level validation efforts, making upgrades and incremental features difficult to validate. The GMP ELN is a COTS (commercial off the shelf) product that facilitates fast deployments and "go-live" operations in cGMP environments. The modular nature of the GMP ELN allows for additional methods, people, and instruments to be simply added with minimal re-qualification required.

GMP Electronic Notebook Architecture

The GMP Electronic Notebook foundational level is comprised of all instrument connections and network access to any required database for actual test method execution by the analyst. These traditionally include CDS systems, document management systems, calibration software systems, CAPA systems etc. Some of the above functions can be implemented within the GMP Electronic Notebook software, however, a typical installation generally requires interfacing with pre-existing software platforms.

This interoperability is a key component of deploying the GMP Electronic Notebook at the foundation level in any quality operation. The architecture can be connected to your network either in hard wired or wireless fashion. In a secure wireless configuration, an analyst can roam throughout the QC area and access all the components of workflow necessary to run a sample. This includes the currently approved revision of the standard test method, instruments used in analysis, and access to databases (chemical inventory, instrument calibration, etc.). Instruments include chromatography instruments and data systems, balances, spectrophotometers, pipettes, even thermometers. Supporting data such as reagent expiration dates and instrument calibration dates are linked to the record at run time. This is key to compliance management in the lab. All data and metadata are captured and stored not on the tablet PC, but wirelessly sent to a secure server installed for the GMP ELN. (Figure 5, next page)

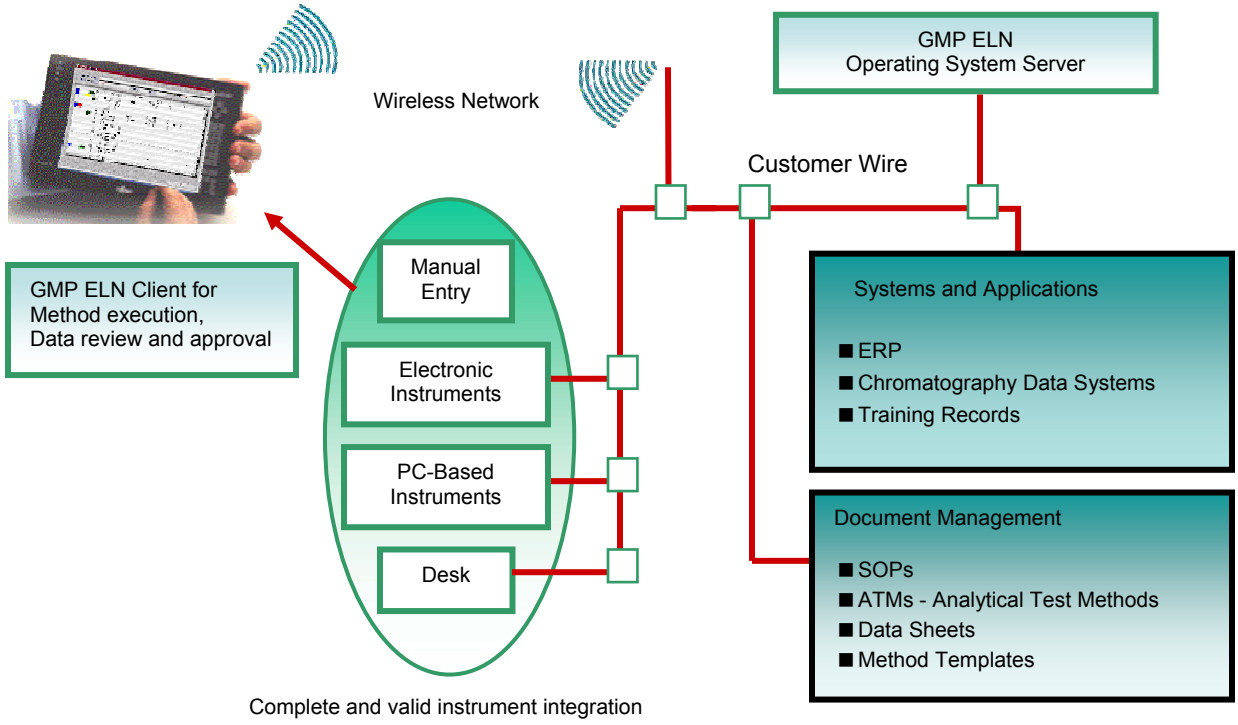

Figure 5

A GMP Electronic Notebook System architecture provides a mobile handheld environment for the analyst to interact with ALL the IT systems necessary for them to complete their lab tasks. They can view the standard test procedure, capture observations and manual data, capture ALL instrument data and metadata...with real-time database cataloging at each method step.

Benefits of a GMP Electronic Notebook Layer in a cGMP IT Infrastructure

To facilitate the "paperless" e-manufacturing environment and to gather consistent quality information while enhancing operational efficiencies, organizations must integrate lab-based workflow automation in concert with their LIMS and ERP layers. This ensures the efficient and productive capture of all method and procedure specific data and metadata in a validated electronic environment.

During routine use of this platform in a validated environment, users chose typical QC processes in simple categories to calculate before/after values and percent savings in resource time. Tasks included:

- Prepare materials and collect results.
- Write-up reports.
- Check & review documentation.
- Approve documentation and results.
- Generate CofA and/or lab report.

Over a six-month time period, the operation experienced savings in most areas, depending on activity and complexity. Overall, the two general results observed were as follows:

- 30% reduction in testing resource requirements
- 50-75% reduction in review/approval time

These metrics clearly show a large productivity gain by going paperless at the analyst and operator levels and using the data (captured in real-time) to automatically populate the data fields within the

higher-order reporting structure (LIMS and ERP). In doing this, the QC lab operation insures compliance with cGMP requirements for electronic data while simultaneously significantly improving productivity and reducing costs. The ultimate benefit of this QC/QA GMP Electronic Notebook System is the reduction in overall cycle times to product release and a "window" into the actual SOP/Method process for any subsequent product/process investigations.

Conclusion

At most life science-based manufacturing companies, management is seeking to improve operational costs and productivity to be competitive and enhance the bottom-line. For decades, most of the data management processes in QA/QC have been "paper-based", requiring numerous non value-added checks to ensure that data integrity and product quality standards have been met. In today's modern computer-based environments, technology can be adapted to totally eliminate these paper systems and replace them with a compliant and fully electronic capture, review and reporting system. In concert with other IT initiatives (e.g. ERP, LIMS, CDS), companies can now adopt a GMP Electronic Notebook data management platform for a paperless GMP Informatics architecture. The notebook fills a niche with a unique capability: the ability to electronically deliver existing approved SOP's to analysts and operators, prompting them to follow the procedure as written, and automatically capture all the method data and outcomes, particularly from instruments. This process eliminates operator errors or transcription problems in working with a typical paper-based notebook.

These analyst-centric operations comprise the GMP Electronic Notebook System layer within the greater cGMP Informatics IT architecture . Within this layer all instruments, including CDS, are interfaced with the cGMP Electronic Notebook System and only processed, filtered and approved cGMP result data is transferred to the LIMS and ERP layers. This process has been shown to reduce testing times by 30% and to reduce review and approval time by 50-75%. In doing so, production can approach real-time release of product yielding significant benefits to the overall manufacturing organization and, in turn, the corporation as a whole.

Going compliantly "paperless" in the GMP quality control/quality assurance environment is now a reality, delivering significant savings in time and money, as well as improvement in professional job satisfaction for valued technical staff. This three-tiered cGMP Laboratory Informatics architecture provides a platform for 21st century production requirements for the pharmaceutical and biotechnology industries.

References:
(1) Proceedings of IMACS 2006, May 17-18, 2006, Princeton, NJ (USA) http://www.imacs-world.com
(2) Proceedings of IMACS 2005, May 18-19, 2005, Princeton, NJ (USA) http://www.imacs-world.com

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