Quality Risk Management

Transforming Quality into a Fundamentally New Approach

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Objectives of this Presentation

- Transforming our approach to quality
- How QRM will help us
- QRM Concepts
- QA/QC Governance Model
- Benefits of QRM
Quality is managed between three constituencies – Management, QC and QA

The Quality Management Triangle

Mgmt Oversight

Quality Assurance (QA)

Quality Control (QC)

“Independent” quality assurance through audits

Quality governance as part of management oversight

Quality control built into business processes
What is a risk and what is Quality Risk Management?

Key Definitions

- **Risk**
  - Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm

- **Quality Risk Management (QRM)**
  - Quality Risk Management (QRM) is a systematic process consisting of
    - Risk identification
    - Risk assessment
    - Risk mitigation
    - Risk avoidance/reduction
    - Communication
  - QRM supports better decision making by providing greater insight into risks and their impacts and helps to make proactive decisions
The objective of quality risk management is to ensure safety of patients and integrity of data.

**Objectives of Quality Risk Management in GCP & Pharmacovigilance**

- **Safety Processes**
  - in all clinical trials and post-marketing surveillance activities

- **Data Integrity**
  - of data created in these trials and activities

**Core Objectives**

- SOP and Regulatory Compliance
- Robust processes
- Consistency across all entities
- Transparency

**Derived Objectives**
Clear need to change our approach to Quality

*Higher expectations of Quality across industry*

**Internal**
- Need for early detection of critical quality issues
- Need for transparency and prioritization of quality risks
- Limitations of current auditing approach, calling for range of new “instruments”
- Need to optimize resources in teams and functions

**External**
- Increasing regulatory pressure
  - More inspections
  - Inspections in new territories
  - New approach to inspections: From trial/clinic-centered to systems review
- Growing media scrutiny of compliance, or lack thereof: Compliance is sustainability factor
Major challenge #1: The numbers are against us

Audits cover only about 2% of clinical related activities

Focus of Risk Mgmt

GCP & Pharmacovigilance Entities

Safety Processes

Data Integrity

- HQ functions: $10^1$
- Affiliates: $10^2$
- Partners: $10^3$
- Trial Centers: $10^4$

250-300 Audits
~20,000 Entities

= < 2% Audit Coverage

QRM Quality Risk Management
Major challenge #2: Rising rate of regulatory inspections

Early detection of risk is essential

Source: Health Authority Analyses (Last update December 21st, 2007)
The FDA encourages Pharma Industry to develop and implement a prospective Quality Risk Management system …

‘Quality Risk Management Initiatives at FDA’

- FDA has the mandate to ensure regulatory compliance, but regulations
  - Set only the floor not the ceiling for quality
  - Should support risk based approaches

- Quality management always should keep the big picture in mind
  - Analyzing the significance/ impact of quality deviations/ risks
  - Detecting and correcting multi-system failures first

- Recommended approach is to develop and implement a “quality system, structured on risk identification and management, that is prospectively shared with and agreed to by FDA”
  - To “utilize the information that we routinely obtain during monitoring/ auditing/ inspection to improve quality”
  - To “conduct signal detection and follow-up”

Source: Adapted from Presentation of David Lepay, Senior Advisor for Clinical Science (FDA), at DIA: 43rd Annual Meeting, Atlanta 2007
Changes in the regulatory environment

- August 2013
  - EMA Reflection Paper on **Risk-Based Quality Management in Clinical Trials**
  - FDA Guidance – Oversight of Clinical Investigations: *A Risk-Based Approach to Monitoring*
- April 2009
  - Q10 Pharmaceutical Quality Systems
- May & June 2006 – ICH guidance documents recommended for adoption
  - **Q9 – Quality Risk Management**
  - Q8 – Pharmaceutical Development
- Originally manufacturing focused but now being applied to the full development process
  - Generic Risk Management Guidelines
  - Applicable to any public, private or community enterprise
- EU GMP - Eudralex Volume 4, Annex 20, Quality Risk Management (2008)
  - Systematic approach to QRM for compliance with GMP and other quality requirements
- ISO 14971 (2007) - Application Of Risk Management To Medical Devices
  - Identify hazards associated with medical devices including in vitro diagnostics
  - To control the risks and monitor effectiveness
ICH Q9 Process

Initiate
Quality Risk Management Process

Risk Assessment
Risk Identification
Risk Analysis
Risk Evaluation

Risk Control
Risk Reduction
Risk Acceptance

Output / Result of the
Quality Risk Management Process

Risk Review
Review Events

Risk Communication

Risk management Tools

unacceptable
Only a new approach to Quality Management will help to cope with these challenges

Fundamental Transition in Quality Management

**Traditional Approach**

- Detection of Individual Quality Issues
  - Sample analysis of quality risks
  - Detail information on individual functions/sites
  - Fragmented fact base on critical quality issues
  - Retrospective

**Future Requirement**

- Detection of Systemic Quality Issues
  - Continuous evaluation of many/all entities and risk areas
  - Focused sets of information on many/all entities
  - Identification of systemic quality issues based on comprehensive set of information
  - Prospective
The traditional approach of quality management which focuses on in-depth, comprehensive but infrequent audits is expanded by new elements: QRM assesses quality data in a more focused and more frequent manner.

**QRM Elements**

- **Depth & “Richness”**
  - Comprehensive
  - Intermediate
  - Selective

- **Frequency & “Reach”**
  - Low: < every 18 months in few entities
  - Medium: every 6-12 months in many entities
  - High: < 3 months in all entities

**Classical Audits**

**Diagnostic Tools**

**Key Risk Indicators (KRIs)**

- Traditional QA
- New QRM Elements
Analytical QRM tools which cover risks across the different entities and phases of clinical trials and safety reporting

Scope of Quality Risk Management (QRM)

- **Clinical Trial by Phases**
  - Start-up
  - Conduct
  - Close-out

- **Study Quality Risk Assessment**
  - Study Quality Risk Assessment

- **Clinical Trial Centers**
  - QRM IM Tool
  - Data Management/Science Review

- **Affiliate/Centers of Excellence**

- **Service Providers/CROs**
  - QRM IM Tool
  - Safety Operations

- **Drug Safety Affiliates**

- **QRM IM Tool**

<table>
<thead>
<tr>
<th>QRM Risk Area</th>
<th>Entity</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Quality Risk Assessment</td>
<td>Study / protocol</td>
<td>Study set-up</td>
</tr>
<tr>
<td>Clinical Trial Centers</td>
<td>Study center/investigator site</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>Data Management/Science Review</td>
<td>Study / protocol</td>
<td>Good Clinical Practice Data quality</td>
</tr>
<tr>
<td>Affiliate/Centers of Excellence</td>
<td>Affiliate</td>
<td>Study Management</td>
</tr>
<tr>
<td>Service Provider/CRO Assessment</td>
<td>Service Provider/CRO</td>
<td>All operational areas (systems, processes)</td>
</tr>
<tr>
<td>Drug Safety in Affiliates</td>
<td>Affiliate</td>
<td>Pharmacovigilance Clinical safety</td>
</tr>
<tr>
<td>Safety Operating Centers</td>
<td>Processing center Med. Eval. Group</td>
<td>Pharmacovigilance Clinical safety</td>
</tr>
</tbody>
</table>
QRM clearly distinguishes itself from traditional quality management

Key Aspects of Traditional Quality Management vs. QRM Approach

<table>
<thead>
<tr>
<th>Aspects</th>
<th>Traditional Quality Management</th>
<th>QRM Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment mode</td>
<td>Ad hoc</td>
<td>Continuous evaluation</td>
</tr>
<tr>
<td>Time resolution</td>
<td>Months - Years</td>
<td>Days - Months</td>
</tr>
<tr>
<td>Coverage (reach)</td>
<td>Limited sample</td>
<td>Comprehensive (all entities)</td>
</tr>
<tr>
<td>Level of detail (richness)</td>
<td>High</td>
<td>High for determined key risk factors</td>
</tr>
<tr>
<td>Data collection</td>
<td>Ad hoc in context of audit</td>
<td>Continuous, through a variety of activities and tools</td>
</tr>
<tr>
<td>Tools</td>
<td>Audit reports</td>
<td>QRM reports, Diagnostic Questionnaires, Key Risk Indicators, IM Tools</td>
</tr>
<tr>
<td># of routine audits</td>
<td>most</td>
<td>few</td>
</tr>
<tr>
<td># of specific audits</td>
<td>few</td>
<td>Most (more focused) ; Confirmatory activities</td>
</tr>
<tr>
<td>Processes</td>
<td>Auditing &amp; CAPA</td>
<td>Full range of QRM processes and proactive mitigation</td>
</tr>
<tr>
<td>Organizational capabilities</td>
<td>Audit &amp; subject matter expertise …</td>
<td>… PLUS strategic risk assessment capabilities</td>
</tr>
</tbody>
</table>
The QRM approach

Quality Risk Management at a Glance

| QRM Concept and Philosophy | ▪ Risk based approach to quality management and related resource deployment  
|                          | ▪ Leverage of all existing data to generate comprehensive risk landscape |
| QRM Processes            | ▪ Proactive identification, transparency, assessment and mitigation of risks and continuous process improvement  
|                          | ▪ Continuous trend and pattern analysis to identify systemic issues |
| QRM Organization         | ▪ Combination of customer orientation (GCP/ pharmacovigilance/ systems and infrastructure) and functional excellence  
|                          | ▪ Active interfaces to business partners through coaching and consulting  
|                          | ▪ Risk information integration and prioritization by customer specific Quality Area Teams |
| QRM Tools and Methodologies | ▪ KRI and tailored set of questionnaire based self-assessment tools and IT supported systems  
|                          | ▪ Standardized framework and approach for risk assessment and integration across entire risk landscape  
|                          | ▪ Standardized procedures and frameworks for risk mitigation and follow-up |
A lot of the information required is already available, however fragmented
Automatic analysis of existing data is the underlying principle for a Continuous Risk Evaluation

Use the existing data... ... to identify areas with increased quality risks

Wealth of Existing Data

Safety data

Trial info

Clinical data

# S/AEs

QRM Dashboard

Allowing for different views:
- Product/Project View
- Process View
- Geographical View
Continuous Risk Evaluation consists of two components – ‘stable’ Base Risk Profile and ‘variable’ Key Risk Indicators

Overview of QRM Calculation Components

- Base Risk Profile (BRP) measures the underlying risk of an entity
- The BRP factors vary over longer time periods
- Therefore, the BRP is updated about once every year
- Key Risk Indicators (KRIs) are calculated on a regular basis

Components:

- Entity
- Risk *
- Impact
- Detectability
- Likelihood

The Base Risk Profile (BRP) measures the underlying risk of an entity. The BRP factors vary over longer time periods, therefore, the BRP is updated about once every year. Key Risk Indicators (KRIs) are calculated on a regular basis.

RPN-Value → Translates into RPN Signal (Risk Priority Number)

For more information, refer to Failure Mode & Effect Analysis.
The calculation logic of the Risk Priority Number is analogous to the calculation logic of a car insurance premium.

**Analogy – Calculation Logic of a Car Insurance Premium**

1. **Base Risk Profile (BRP)**
   - ~ Basic Car Insurance Premium
   - e.g. Demographics
   - e.g. Car (Class)
   - e.g. Location

2. **Modification of Score**
   - Key Risk Indicators (KRIs)
   - ~ Number of Incidents: e.g. Car Accidents

3. **Risk Priority Number (RPN)**
   - ~ (Individual) Car Insurance Premium
KRIs are assigned to risks, likelihood or detectability, and have predefined predictive value – 3-fold classification/ digital nature

Assignment of KRIs

<table>
<thead>
<tr>
<th>Risk-KRI allocation</th>
<th>Allocation of the Predictive Value to Risks</th>
<th>KRIs to Likelihood / Detectability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks</td>
<td>Relevance</td>
<td>KRI</td>
</tr>
<tr>
<td>Safety Processes</td>
<td>Expert Judgm.</td>
<td>SOPs / int. guide</td>
</tr>
<tr>
<td>Data Integrity</td>
<td>Evidence</td>
<td>M</td>
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<td>Direct Indicator</td>
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<td>Indirect Indicator</td>
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- Not all KRIs are relevant for each risk
- Not all KRIs have the same predictive power
- KRIs are either linked to predict a change in the likelihood or the detectability of risks
Clinical Trial Centers
Imagine the thoughts of a study manager

- Is monitoring sufficient and on time?
- Is patient recruitment well managed?
- Was site training sufficient?
- Are inclusion criteria followed?
- Is the CRF clear enough?
What does she do to find out?

Where can I find all this information on enrollment rates?

What do I have to address first?

Where is the information on protocol violations?

Which monitoring report do I have to read?
  Is there a summary available?

How many data discrepancies have been reported?
The usual issues are:

- Number of data queries above average
- Delayed monitoring or missing site visits
- Unusual high rate of enrollment
- Too many protocol violations
- Over enrollment or no enrollment at all
- No Adverse Events reported
- High number of premature terminations
Examples of key risk indicators developed in order to manage quality risks in conduct of clinical trials

Clinical Trial Centers – Key Risk Indicator Landscape

- **Site Activation**
  - Activation
  - KRI: Delayed Enrollment

- **Patient Recruitment**
  - First Patient
  - 2 KRIs:
    - Delayed/No 1st Mon. Visit
    - Inclusion Criteria
    - Fast Enrollment Over-Enrollment

- **Treatment**
  - Monitoring
  - KRI: Data Discrepancies
  - 2 KRIs:
    - Protocol Execution
    - # Protocol Violations

- **Study Mgmt**
  - Data Mgmt
  - Compliance Monitoring
  - KRI: Early Terminations
  - 2 KRIs:
    - Safety Mgmt
    - KRI: AE Reporting

- **Patient Discharge**
  - Termination
  - Reg. Authorities
Risk Indicator: Monitoring Visits delayed

Is monitoring sufficient and on time?

Study: XYZ  Risk Indicator: Delayed Monitoring

<table>
<thead>
<tr>
<th>Clinical Trial Center</th>
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</table>

- Monitoring within 10 Weeks After first patient enrolled or previous monitoring visit

Illustrative
Risk Indicator: Premature Terminations above Protocol Average

Is there an unusual high rate of early unexpected patient drop-outs at any site?

Study: XYZ

Risk Indicator: Premature terminations of patients¹)

Measures average drop-out per patient for a site against the protocol average

Threshold → 1.3 x Protocol Average

Protocol Average

Clinical Trial Centers

¹) excl. death, illness,...
The result of the assessment is available in a dashboard

<table>
<thead>
<tr>
<th>Study XYZ</th>
<th>Risk Indicator Dashboard</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>May-06</td>
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<tr>
<td>AE Reporting</td>
<td>● ●</td>
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<tr>
<td>Data Management Discrepancies</td>
<td>● ●</td>
</tr>
<tr>
<td>Premature Terminations</td>
<td>● ●</td>
</tr>
<tr>
<td>Protocol Violations</td>
<td>● ●</td>
</tr>
<tr>
<td>No First Monitoring Visit</td>
<td>● ●</td>
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<tr>
<td>Delayed Monitoring Visits</td>
<td>● ●</td>
</tr>
<tr>
<td>Fast Enrollment</td>
<td>● ●</td>
</tr>
<tr>
<td>Over-Enrollment</td>
<td>● ●</td>
</tr>
<tr>
<td>Delayed Enrollment</td>
<td>● ●</td>
</tr>
</tbody>
</table>

Clinical Trial Centers No. 1234
Month Year
Study XYZ
Key Risk Indicators allow cross-center comparison of GCP risks

Example: Comparison of Clinical Trial Centers across regions regarding Protocol Violations

<table>
<thead>
<tr>
<th>“Protocol violations”</th>
<th>Description</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol violations</td>
<td>Higher than average number of protocol violations</td>
<td>Possible indicator for inadequate monitoring, site-staff training, resources or workload</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th></th>
<th>Affiliate 1</th>
<th>Affiliate 2</th>
<th>Aff. 3</th>
<th>Aff. 4</th>
<th>Affiliate 5</th>
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</table>

Threshold (>1,2)  Ratio

Example: Comparison of Clinical Trial Centers across regions regarding Protocol Violations.

Clinic Trial Center
QRM can monitor each trial for systematic quality risks

Are there any systematic quality issues within this study?

Share of Clinical Trial Centers with high risk signals in Country A

- Protocol Violations: 11%
- Delayed Monitoring: 22%
- Fast Enrollment: 5%
- No Monitoring: 2%
- Delayed Enrollment: 2%
- Early Terminations: 13%
- Over-Enrollment: 5%
Drug Safety/Pharmacovigilance
Examples of Key Risk Indicators in Pharmacovigilance

Drug Safety – Key Risk Indicator Landscape

Input Channels

- Literature
- Phone
- Fax
- Mail
- email

KRI Channel Mix
KRI Follow-ups

Affiliate

- ADR reports
- Local Labels
- Local SOPs
- QC process
- Trng of DS staff

KRI ADR reports
KRI Variance of #AEs
KRI Data completeness, etc.
KRI Label Conflicts
KRI SOPs in line
KRI Data Corrections
KRI Training

Global Drug Safety

- ADR reports
- CDS
- Global SOPs
- QC process
- Trng of DS staff

KRI Pending reports
KRI Changed submission decision

Affiliate

- ADR reports

Reg. Authorities

KRI Late Reporting
KRI Subm.
Late submissions of 15-day reports

15-day submissions late and locally delayed

Comment

- Key Risk Indicator measures the share of 15-day reports submitted late that resided at the affiliate for more than 3 calendar days (late AND locally delayed).

- From April – July the affiliate delayed 15-day submission reports above the acceptable level of 2% indicating a significant affiliate contribution to late submissions.

- Since August, no additional red signals have been received indicating no significant contribution to late 15-day submissions.
Continuous high variance in AE reporting by an affiliate represents a high risk of non-compliance.

Relative number of spontaneous ADRs collected at the Affiliate

At various time points the variance in the AE collection rate at the affiliate shows a higher than expected variance indicating erratic collection patterns.

QRM Signal: higher or lower than expected variance in AE collection.
On the KRI level, the results of the QRM assessment will be summarized per affiliate in a dashboard.

<table>
<thead>
<tr>
<th>KRI</th>
<th>Short Description</th>
<th>Results for XX affiliate – 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>003</td>
<td>Case key field completeness</td>
<td>Jan: Green, Feb: Green, Mar: Green, Apr: Green, May: Green, Jun: Green, Jul: Green, Aug: Green, ...</td>
</tr>
<tr>
<td>009</td>
<td>Late and delayed submissions</td>
<td>Jan: Green, Feb: Green, Mar: Green, Apr: Green, May: Green, Jun: Green, Jul: Green, Aug: Green, ...</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>Jan: Red, Feb: Red, Mar: Red, Apr: Red, May: Red, Jun: Red, Jul: Red, Aug: Red, ...</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>Jan: Red, Feb: Red, Mar: Red, Apr: Red, May: Red, Jun: Red, Jul: Red, Aug: Red, ...</td>
</tr>
</tbody>
</table>

- Red signal
- Green signal
- Data not available
Governance
Depending on the RPN signal, mitigating actions need to be defined and documented

<table>
<thead>
<tr>
<th>Risk Report Signaling</th>
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</thead>
<tbody>
<tr>
<td>▶ The overall risk level, indicated by the value of the <strong>RPN (Risk Priority Number)</strong>, can be either</td>
</tr>
<tr>
<td>- high (=red signal)</td>
</tr>
<tr>
<td>- medium (=yellow signal)</td>
</tr>
<tr>
<td>- low (green signal)</td>
</tr>
<tr>
<td>▶ RPN is calculated for “Safety Processes” and “Data Integrity”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mitigating Actions (Recommended Approach)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Mitigating actions are tracked and documented. Details are entered regarding concrete root causes and risk responses and are completed for all high risk KRIs of an entity which has a red RPN, implying high risk level</td>
</tr>
</tbody>
</table>
A data-driven risk assessment process represents the backbone of QRM - other generic processes support it.
7 Step Process includes Key Interfaces with Business Partners

- Strategic Focus of QRM to achieve **quality by design** as a core company business process.
- Communication with and involvement of Senior Functional Management, outside of “Quality”, in how and where QRM is applied.
- Role of **Quality Area Teams** throughout the whole process to manage interactions and communication between quality and business process owners.
- Ongoing development and monitoring of **Quality Area Plan**
- Single decision maker and accountability.
The Quality Area Team drives the process

Quality Area Team (QAT) Concept and Key Responsibilities

- Has full accountability for quality risk management activities within quality area
- Liaises with Quality Area Head to align risk identification and mitigation activities overall

QAT Leader

- Ensures that quality risks are identified and analyzed (e.g. assesses all audit requests)
- Defines mitigation actions (e.g. audit prioritization) and consults functional experts
- Writes, maintains and tracks Quality Area Plans (QAP)
- Is the key quality contact to business partners: coaches & consults business partners in risk identification, analysis and mitigation

Functional Experts (ad hoc)

- Provide functional expertise along the entire Process
- Continuously reviews and provides input into risk evaluations & definitions of mitigation actions
- Interacts with business partners for operational preparation of mitigation actions defined by QAT

Auditor / Quality Risk Analyst / CAPA Coordinator

- Closely collaborate in risk identification and analysis, as well as in the definition and execution of mitigation actions

Business Partners (risk-bearing entities)
Each Quality Area is sub-structured into several Quality Area Teams (QAT) according to the key areas of activity.

### Overview of QATs per Quality Area

<table>
<thead>
<tr>
<th>SAFETY QATs</th>
<th>CLINICAL TRIALS QATs</th>
<th>ENTERPRISE SYSTEMS QATs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Safety in Affiliates</td>
<td>Early Development</td>
<td>Internal Systems</td>
</tr>
<tr>
<td>Safety in Operations Centers</td>
<td>Late Development</td>
<td>External Systems</td>
</tr>
<tr>
<td>Safety Partnership &amp; Agreements</td>
<td>Medical Affairs</td>
<td>External Alliances</td>
</tr>
<tr>
<td>Safety Science</td>
<td>Affiliates</td>
<td>Service Providers</td>
</tr>
</tbody>
</table>
The benefits of the QRM system include early detection, broader reach and deeper insights with regard to quality risks.

**Benefits of QRM**

**Category**
- Early Detection
- Broader Reach
- Deeper Insights

**Benefits**
- Time To Correct
- Avoided Costs
- Protected Image
- Comprehensive Issue Detection
- Quantifiable Overall Exposure
- Focused Allocation of Resources
- Central & Local Issues Differentiated
- Trends and Patterns Identified
- Process Improvements
Only a phased approach can ‘make it happen’

Select Pilot & Team

Develop Concept

Develop Processes & Interfaces

Develop IT-Tool & Automated Data Feeds

Roll-out

Integrate
Thank you!

For additional information or questions about this material, please contact:

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