

Open Source as a Strategic Enabler for EMA Submissions: An R Shiny Approach

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Agenda

1. Introduction
2. RMP Table Requirements
3. Why Open Source
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Introduction - Regulatory Context

- Risk Management Plans (RMPs) are a core component of submissions to the European Medicines Agency (EMA)
- RMP Tables support benefit - risk evaluation throughout a medicinal product's lifecycle
- Frequent updates are required as safety data evolves across development stages

Introduction - Operational Challenge

- RMP tables must be repeatedly generated across:
 - Multiple assets
 - Multiple submission cycles
- At scale, traditional table development approaches become **timeline-intensive**:
 - Remediation for study-specific needs is frequently required
 - Table programs are often rewritten for each submission

Problem Statement



How can we:

Maintain regulatory alignment?
Improve efficiency and consistency?
Scale RMP table generation across assets?



Opportunity to modernize workflows using open-source technologies

RMP Table Requirements: Clinical Exposure

- Clinical exposure should be summarized at an aggregated level and across all indications in the RMP
- Key elements commonly reported include:
 - Number of exposed subjects
 - Duration of exposure
 - Total person-time
- Subgroup exposure summaries (e.g., by age group and gender, or by race) may be required to support interpretation of safety findings

Cumulative for all indications (person time)		
Duration of exposure	Patients	Person time
<i>e.g. <1 m</i>		
<i>1 to <3 m</i>		
<i>3 to <6 m</i>		
<i>≥6 m etc.</i>		
Total person time		
<Indication>		
Duration of exposure	Patients	Person time
<i>e.g. <1 m</i>		
<i>1 to <3 m</i>		
<i>3 to <6 m</i>		
<i>≥6 m etc.</i>		
Total person time for indication		

RMP Table Requirements: Adverse Events

- Safety summaries are a core component of RMPs
- Adverse Events should be summarized by:
 - Severity
 - Seriousness
 - Relevant clinical groupings
- Although no specific statistical metrics are mandated, common metrics to support product safety may include:
 - Comparative risk measures
 - Exposure-Adjusted Incidence Rates (EAIRs)

AESI category Preferred Term [a]	Active (N=XXX)		Comparator (N=XXX)		Difference of Risk (Active - Comparator)		Relative Risk (Active / Comparator)	
	EAIR/ 100 Pt-yr [b]	95% CI	EAIR/ 100 Pt-yr [b]	95% CI	Difference	p-value [c]	Ratio	p-value [d]
AESI Category Name #1	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
Preferred Term #1	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
Preferred Term #2	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
AESI Category Name #2	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
Preferred Term #1	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
Preferred Term #2	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
AESI Category Name #3	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
Preferred Term #1	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
Preferred Term #2	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
AESI Category Name #4	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
Preferred Term #1	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx
Preferred Term #2	xx.x	(xx.x, xx.x)	xx.x	(xx.x, xx.x)	xx.x	0.xxx	xx.x	0.xxx

Treatment-emergent adverse events include adverse events that started between the date of first dose and xx days after the date of last dose. A preferred term may be seen in multiple AESI categories.

[a] Coded using MedDRA version xx.x. A subject is counted only once for multiple events within preferred term/ AESI category.

[b] EAIR per 100 subject-years is defined as 100 times the number of subjects with the specific event divided by the summation of time, in years, to first AE for each subject among subjects included in the analysis. If a subject had no AE, the time to first AE will be defined as the subject's total treatment duration in days. Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator.

[c] P-value based upon a Wald chi-squared test.

[d] P-value is calculated using a modified Poisson regression approach (Zou G., Am J Epidemiol 2004; 159(7):702-6).

The calculations of incidence rate and associated confidence interval can be found in (Liu, et al., Statistics in Medicine, 2006; 25:1275-1286).

Why Open Source and R Shiny?

RMP table generation is:

- Required across multiple assets and EMA submission cycles

An application-based, open-source approach enables:

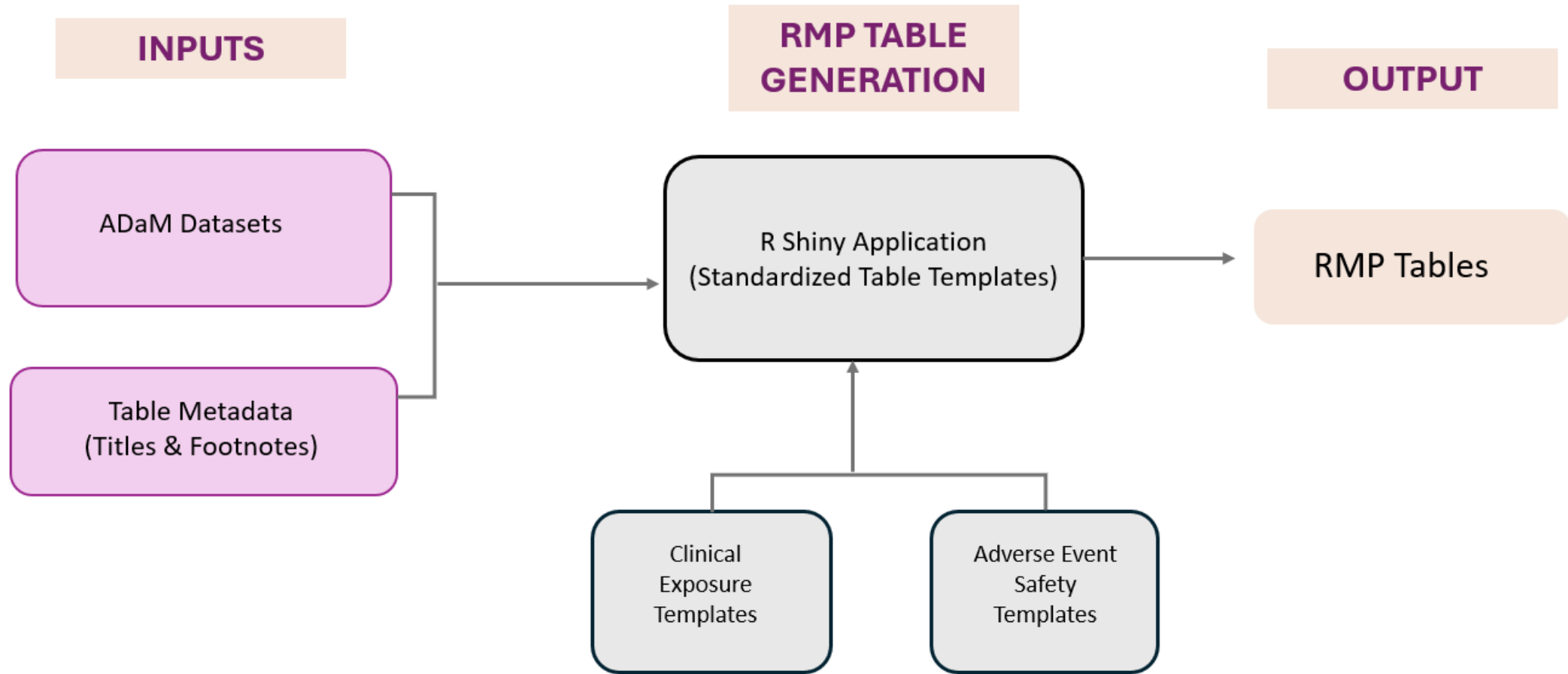
- Standardized table layouts and calculation logic
- Reuse across programs while maintaining regulatory alignment

R Shiny was selected to:

- Allow non-R users to generate tables through a controlled interface
- Preserve flexibility for advanced customization when needed

This approach improves efficiency and consistency without disrupting established validation workflows

RMP Application Overview



RMP Application - Data Inputs and Standardization

ADaM datasets:

- Provide standardized variables and parameters
- Minimize table-specific derivations

Metadata maintained separately:

- Enables reuse of table structures
- Supports asset-specific context

RMP Application - Architecture



Modular R programs



Each Module:

Implements a predefined table template
Applies standardized calculations and
formatting



**Centralized logic reduces
variability**

RMP Application: Validation Strategy

1. Validation aligned with existing practices:
 - Traditional double programming
2. Application generates XPT datasets for table outputs
3. Independent SAS programs:
 - Recreate summaries from same ADaM inputs
 - Discrepancies investigated and resolved

RMP Application - Considerations and Future Enhancements

- *golem* structured implementation
 - Allows for R package structure
- Unit Testing with *testthat* and *shinytest2* will strength confidence in table generation logic
 - Over time, we may reduce reliance on double programming for certain outputs
- GxP-compliant R environment required
- Key Elements
 - Log files to support audit trails
 - Use of Validated R packages



What did we gain?

Reduced RMP
Tabled
Development
Efforts

Eliminated
asset-specific
table
programming

Faster
regeneration of
RMP tables

Improved EMA
submission
timelines

Organizational Adoption



Adopted across multiple assets



Integrates seamlessly with SAS-based validation workflows



Continuous feedback supports incremental improvements

Thank you

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