TOPRA Module 1 – Strategic Planning in RA

The Relationship between Regulatory Affairs and Project Planning

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Learning Outcomes

- **Know the RA professionals' tasks in project planning**
- **Understand how to organise Regulatory Project Planning and submission Planning**
- **Insight of Common Difficulties & Practical Aspects & Project Risks**

Disclaimer

This presentation is meant to give you an overview but does not focus on the very details on the topics addressed.

Sentences written in italic indicate that the information has been cited from sources referenced in the squared brackets.

Views expressed in this presentation are my personal views and do not reflect the view or policies of any employer or RA organization.

Bringing a new product through various stages of product development is a mammoth task [1]…

Receiving then a license is a big step forward …

Work does not end with the grant of a license…

…it‘s just the beginning of the Life Cycle of a medicinal product

RA professionals' important role in project planning & drug development

- **Advise & support: put ideas into practice and products on the market**

- **Knowledge of regulatory environment** (current & <u>future</u> regulatory requirements)

- **Provide strategic, tactical and operational direction**

- **Ensure successful regulatory strategy <u>to meet the patients' and companies needs</u>**

Today's potential

Roles & Responsibilities of RA professionals

- Ensure compliance with current regulations/ legislations at every stage of product development
- Work with Regulatory authorities
- Recommend and advise on regulatory requirements & strategies
- Support expedite development by working within the regulations (consider future changes)
- Project/ Submission Planning
- Getting more and more involved in business

… **all to support the development/ maintenance of safe & effective medicinal products**

Today's potential

Roles & Responsibilities of RA professionals

- Draft Product Information (regular revisits & revisions required) - xTPP
- Clinical trials (global) – advise on countries, give input on numbers of patients per region, etc.
- Advice on Licensing Strategy (global, US vs EU), → Presubmission requirements
- Contact and cooperate with authorities already during development (SA, presub. meetings)
- Compilation of a "global dossier" for licensing applications together with the respective experts

… all to support the development/ maintenance of safe & effective medicinal products

xTPP …
Vision of the role of the QTPP

On overall overview of the key aspects of the product supports the overall development and helps project teams to follow the agreed strategy and meet at the end the target defined at the very beginning. An important aspect in this context is also to raise the question whether the product would ever be profitable.

Clinical Target Product Profile → Need to be interlinked if different patient target groups → **Quality Target Product Profile** → **Critical* Target Product Profile** ← **Prior knowledge**, **Decision on formulation and process**

Focus Patient
Usage
Population
Dosage (e.g. regimen, form)
Route of administration
Pharmacokinetic characteristics
Strength
Supply/ Storage
Handling

Focus Patient
Appearance
Identity
Assay and Uniformity
Purity/ Impurity
Stability
Delivery/ release characteristics
Bioavailability
Microbiological limits/ sterility

Focus Pharmaceutical Development**
Appearance
Identity
Assay and Uniformity
Purity/ Impurity
Stability
Dissolution/ release
Microbiological limits/ sterility

Business considerations:
Market/ Costs

Would the product ever be profitable?

Source: MSc Dissertation
Elke Hofer-Litzlbauer, 2014

Today’s potential

Roles & Responsibilities of RA professionals

TOPRA

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- Advice on Licensing Strategy (global, US vs EU), → Presubmission & dossier requirements
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… **all to support the development/ maintenance of safe & effective medicinal products**

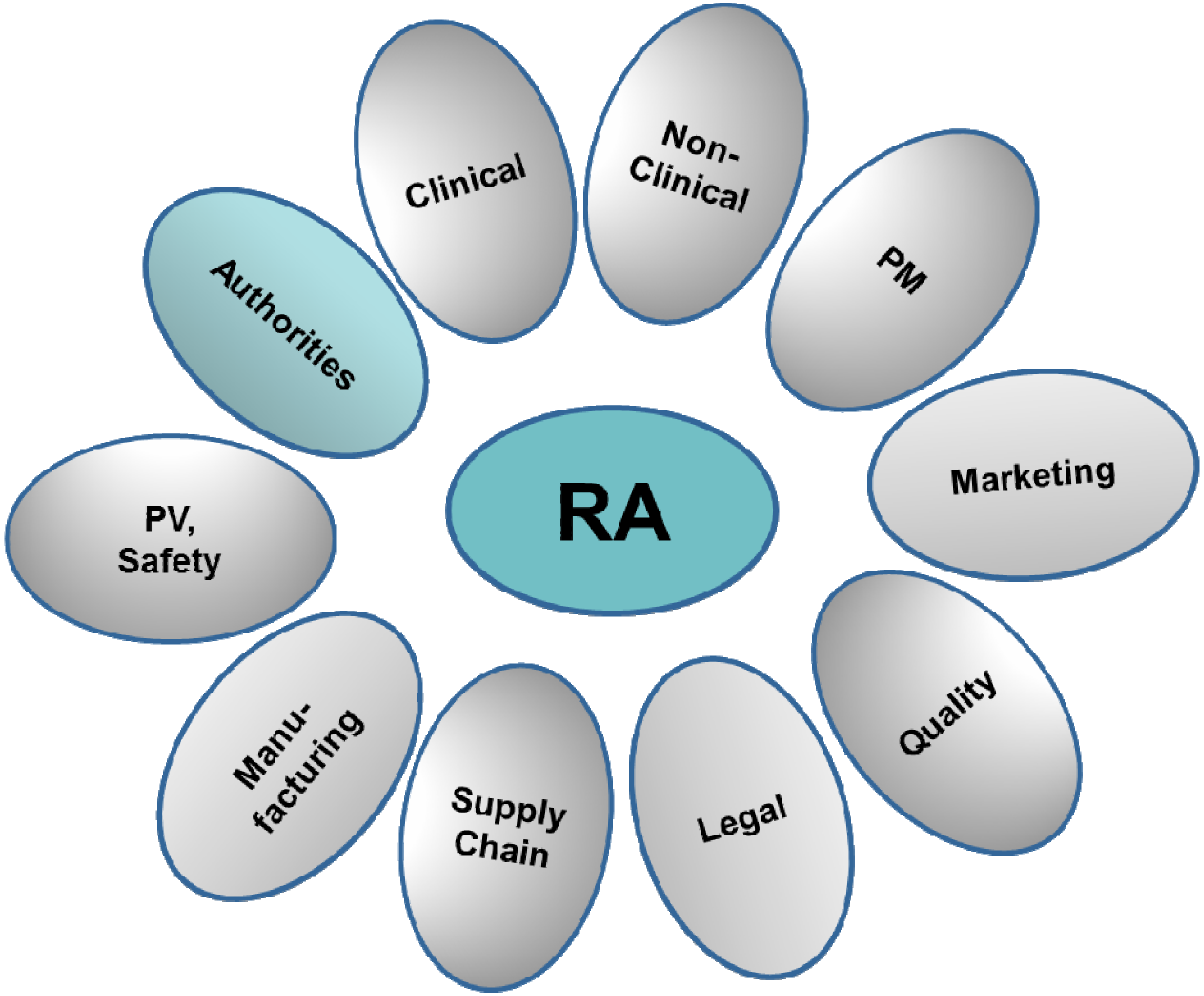
Today’s potential

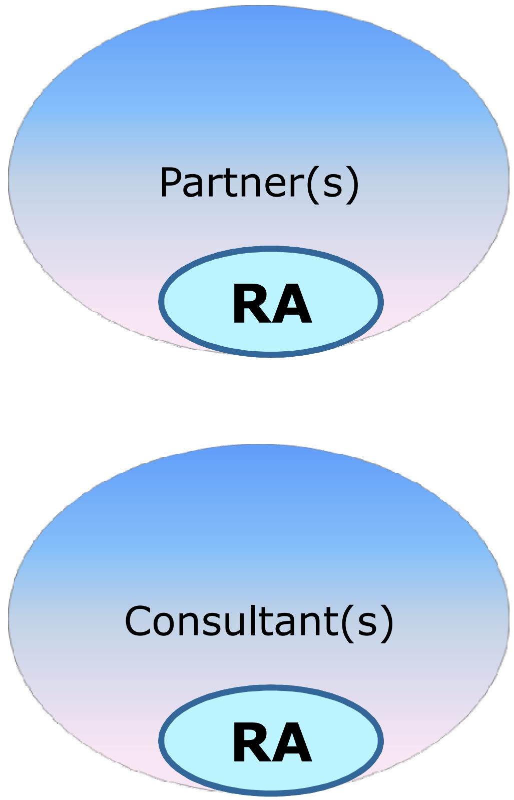
Roles & Responsibilities of RA professionals

- Prior to submission:
  - Manage presubmission activities
  - Inform project team about procedural details & timing
- During MAA procedures:
  - Drive preparation of responses (incl. strategy)
  - Organise meetings/ TCs with assessors
  - Be prepared for Oral Explanations
  - Last minute labeling negotiations & commitments (post approval)
- Prepare back up plans (+gap analysis)

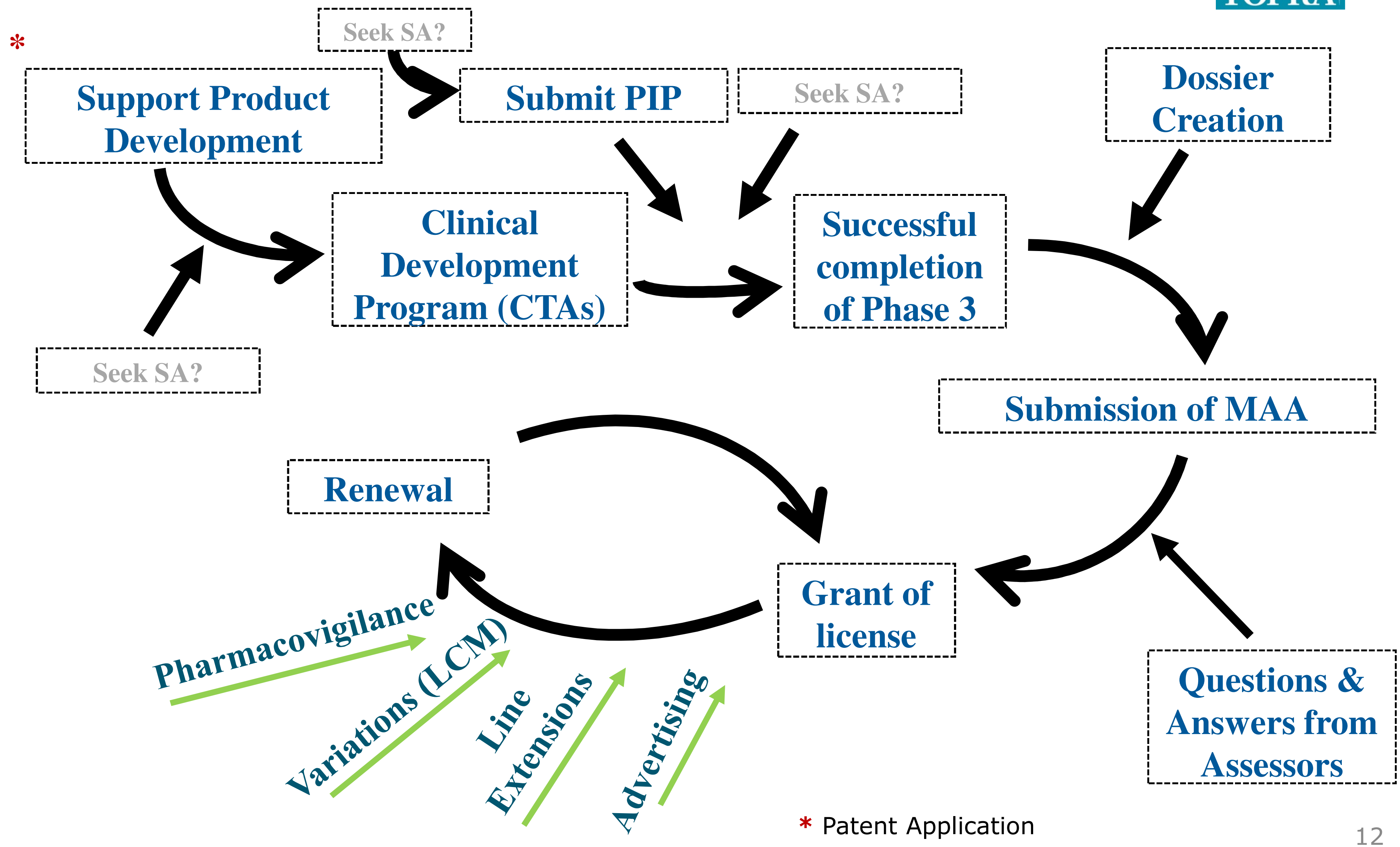
… **all to support the development/ maintenance of safe & effective medicinal products**

RA needs to interact with all functions





RA projects…
one Integrated Drug Development?



* Patent Application

Regulatory Strategy …

… defines the plan for developing the product with the goal of obtaining regulatory approval in desired markets and life-cycle management post approval [2]

… is a formal document that aligns the regulatory activities to bring a new or modified product to market with the business strategy for a product. It provides overall definition and direction to project team for the product being developed by identifying the important regulatory elements to be addressed to market the device [3]

Regulatory Plan…

… *is a document that describes the specific steps and action required to successfully meet the regulatory strategy objectives It contains specific elements required to assemble the regulatory submission. Some key components … [3]*

RA strategy/plan
What needs to be considered?

A good plan is key for successful & profitable projects (incl. timelines, resources, roles & responsibilities …)

- Cross-functional TEAMWORK
- Product development roadmap/ Target Product Profile
- Decision Tree Diagrams
- SWOT Analysis
- Authority feedback (SA, presubmission meetings, etc.)
- Regulations, Directives, Guidelines, etc.
- Commercial/ business needs
- Post-approval LCM activities
- Involve the right functions/ people

Project Planning/ Regulatory Project Management

Project Management is the application of knowledge, skills, tools, and techniques to a broad range of activities in order to meet the requirements of the particular project [3].

For RA projects this means, team members need to:

- Understand the aim of the project - why is the company/team going to do that – project strategy?
- Global Regulatory (strategic) Plan - written (living) document
- (Detailed) Submission Planning document
- Have the required knowledge & expertise & skills (→ listening, communication, pragmatic & analytical)
- Proactive, goal-oriented, “flexible”, in time …

Project Planning/
Regulatory Project Management

Project Management is the application of knowled... ...lls, tools, and techniques to a broad ran... ...der to meet the requir...

The 5 "easy" major steps to ensure effective projects:

1. **Initiating**
2. **Planning**
3. **Executing**
4. **Controlling**
5. **Closing**

- (... Planning document
- Have the required knowledge & expertise & skills (→ listening, communication, pragmatic & analytical)
- Proactive, goal-oriented, "flexible", in time …

Pharmaceutical Project Planning what to start with? Who? How?

“xTPP(s)”

= format for a summary of a drug development program described in terms of labeling concepts [5] = product specifications [6]

to

- prioritize key features & attributes of the target drug product [7]
- facilitate discussions/understanding between agency & applicant
- minimize the risk of late-stage product failures
- increase availability of optimal safety & efficacy data in time
- improve labeling content [5]
- decrease the overall drug development time
- be used throughout the drug development process

Target Product Profile(s)

The TPP should begin with the goal in mind…

it should be a dynamic summary which changes as knowledge of the product increases… ideally, the draft labeling submitted with a new application should be similar with the final version of the TPP…

… prepared by all functions involved in product development lead by Project Management

Target **P**roduct **P**rofile**(s)**

Indications and Usage

Dosage & Administrations

Dosage Forms & Strengths

Contraindications

Warnings & Precautions

Adverse Reactions

Drug Interactions

Use in Specific Populations

Drug Abuse & Dependence

Overdosage

Description

Clinical Pharmacology

Nonclinical Toxicology

Clinical Studies

References

Info on administration

Storage conditions

Patient Counseling Info

FDA, Guidance of Industry, Target Product Profile *[3]*
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf

Draft TPP – an example

Features	Minimum Requirements	Target Requirements (Base Case)	Optimal Requirements	Key Competitor (Best in Class – Currently on Market)
Indication	"XY" in adults	"XY" in both adults and children	"XY" in adults and children in the US & EU	
Efficacy	Same as target =>	Significant Reduction of serious phase/ events	No reported of serious phase/ events	
Safety	Fewer systemic AEs vs. existing IV Better local tolerability vs. Competitor (<70% patients experiencing local AE)	Fewer systemic AEs vs. existing IV and/ **new route administration…** Better local tolerability and systemic tolerability competitor (<50% patients experiencing local AE)	<= Same as Target Much better local and better systemic tolerability vs. Competitor (<30% patients experiencing local AE)	Competitor XY
Dosing / Bioavailability	Same as target => EU: 200% of monthly dose (similar to Competitor). US: 200% of monthly dose	**every other day or weekly dosing.** EU: No dose adjustment. US: Less dose adjustment than Competitor	<= Same as Target No dose adjustment	"conventional" dosing
Ease of Use / Sizes & Needles	Same as target =>	**Device 1 or Device 2** Sizes: 5ml with needle for peds; 10ml with needle for adults **Simple Process:** normal administration **no additional equipment required**	**Device 1** Sizes: 5 and 10ml with needle for peds & adults <= Same as Target	Conventional administration requiring Devices 1 & 2
Packaging	Same as target =>	Special Pack for protection; sterility barrier not required. to be packed in unit carton with PI	<= Same as Target	Competitor, glass vials (various sizes)

Who?
Required functions

Regulatory Affairs

Global Clinical R&D

Quality Assurance

Global Marketing

R&D - Pharmaceutical Development

Partners

Consultants

Stability – Analytical

Finance

Global Medical Affairs

Legal

Pre-Clinical Research

Supply Chain

Project Management

etc.

Regulatory Plan/ Strategy document - structure

1. **TOC**
2. **Purpose**
3. **Background**
4. **Associated Documents**
5. **Product Description**
6. **Registration Plan (worldwide/ region/ country)?**

   Presubmission requirements (GMP certificate, Marketing Authorisation, DMF, PMF, PIP, SA CPP, RUT, format requirements etc.)

7. **Labeling Plan**
8. **CMC Plan (region/ country specific)?**

Regulatory Plan/ Strategy document - structure

9. Clinical Plan (region/ country specific)?
10. Risk Management
11. Lifecycle Management Plan
12. Submission Administration
13. Regulatory Submission Contents & Responsibilities
14. Open Topics
15. Revision History
16. Appendices

→ **Keep information clear, concise & understandable**

→ **Keep "template" up to date**

→ **Keep the project team updated**

Submission Planning (1)

Prior to submission

- Global filing strategy
  - US, EU, Japan, ROW
- Presubmission activities?
- Prerequisites available?
- Procedural aspects
  - timetables?
  - receipt of questions
  - clock stops, one global dossier
  - communication between authorities?

Submission Planning (2)

Prior to submission

- Dossier requirements? (eCTD, NeeS, ASEAN) + region/country specific extras
  - Break the planning down to sections (dependencies)
  - Legacy docs? Still state of the art? Compliance with current regulations? Format requirements?
  - Roles & responsibilities: clear assignment & seek agreement
  - Track identified gaps during creation
- Publishing requirements? (eCTD ≠ eCTD)
  - QC
  - use of portals?
  - Print outs?

Submission Planning (3)

After submission

- Positive validation?
  - yes: start of procedure
  - no: provide requested data/ info (team availability!)
- Gap analysis, generate data upon identification
- Response strategy & process
  - consider clarification meeting(s) with regulators
  - Oral Explanation/ Hearing?
  - Labeling negotiations
- End of procedure (translations, closing sequence, review of official communication (confidentiality)

Submission Planning (4)

Upon approval

- Reimbursement discussions (country specific – start even earlier)
- Launch activities (need to be planned and prepared far ahead approval – to be ready on Day “X”)
- PAC
- Maintenance / LCM
- Extension of Indications

Common Difficulties

- Tight timelines
- Budget limitations
- Resource constraints
- Lack of communication
- Missing prioritization
- Missing skills
- Personal situation

Some recommendations…

- Project Plan, Submission Planning document are living documents → easy to understand & accessible for the team concerned
  - start at the development state and with goal in mind
  - document major decisions
  - consider rapid changes of regulatory environment
  - any changes – (long term) evaluate consequences
  - Gantt Chart: include dependencies of individual tasks
- Communication - share information, updates required (regular core team meetings – Meeting Minutes!)
- Kick Off meeting
- Roles & responsibilities: clearly assigned & seek agreement
- Etc.

Potential risks

Potential risks need to be well understood to act accordingly:

- Avoid
- Transfer
- Mitigate
- Accept

Common risk factors:

- Spare SA on the benefit of time
- Generation of data: at minimum costs versus minimize time
- Submission of insufficient data packages and providing missing data during the procedure

- Etc.

Even though potential risks have been well assessed…

Totality of data

✓ CMC data
✓ Non-clinical data
✓ Clinical Phase 1-3

- 8 major concerns on Day 120
- still for major concerns on D180

- drohende Rejection…

?RA? How to proceed

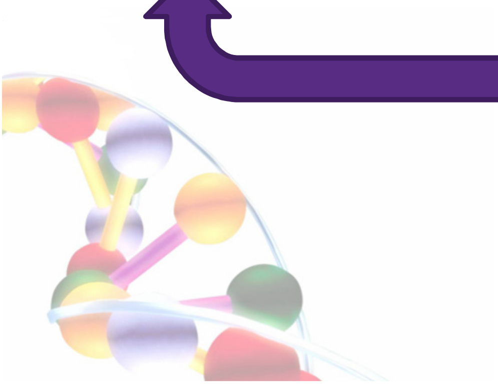
- clarification meeting D120 questions
- add. data generated
- proposal of restricted label

?RA? How to proceed

withdraw MAA ?

?

proceed ?



Even though potential risks have been well assessed…

TOPRA

Totality of data	✓ CMC data ✓ Non-clinical data ✓ Clinical Phase 1-3 • 8 major co… 120 • sti…	…0 …ow to proceed	…ndraw MAA ?

?

proceed ?

✓ submission of MAA
✓ 178 Questions on Day 120
✹Upper Management – withdrawal?
* Open & transparent communication
✓ Support communication between authorities

✓☺ Positive Opinion & approval without any post-approval commitment…

In This presentation we covered

- **Importance & roles of RA professionals**
- **Integrated Drug Development**
- **Regulatory Project Planning**
  - Global Regulatory Plan
- **Submission Planning**
  - Submission Planning Documents
- **Common Difficulties & Practical Aspects**
- **Project Risks**

References

- [1] RA Professional Development Framework, an Overview, RAPS, available from URL: www.raps.org
- [2] Powell S., A Successful Transition to CTD and eCTD, Regulatory Affairs Journal Pharma, 28 September 2007,
- [3] MDDI Medical Decive and Diagnostic Industry News Products and Suppliers, M. Santalucia, 09 July 2012; available from URL: www.mddionline.com, last accessed 28 November 2014
- [4] Pharmaceutical Project Management, 2nd edition, edited by Tony Kennedy, published by Informa Healthcare USA INC, 2008, Chapter 7
- [5] Guidance for Industry and Review Staff, Target Product Profile – a Strategic Development Process Tool, FDA draft guidance, March 2007
- [6] WHO; TPP for the Advance of Market Commitment (AMC) for Pneumococcal Conjugate Vaccines, available from: URL: http://www.google.com/url?sa=t&rct=j&q=Target+Product+Profile&source=web&cd=4&ved=0CGMQFjAD&url=http%3A%2F%2Fwww.who.int%2Fimmunization%2Fsage%2Ftarget_product_profile.pdf&ei=8DXKT5WRBOmO4gSah_AK&usg=AFQjCNG_a0JhZ8gTHK3HHr-RHdEmnDa9kA&cad=rja
  last accessed on 28 November 2014

References

- [7] The Target Product Profile as a Planning Tool in Drug Discovery research, S. Curry and R. Brown, Business Briefing, Pharmatech 2003, available from: URL: www.touchbriefings.com

QUESTIONS?

Picture - Source: CLIPART illustration.com

Abbreviations (1)

AE	Adverse Event	LCM	Life Cycle Management
ASEAN	Association of Southeast Asian Nations	LOI	Letter of Intent
CMC	Chemical,Manufacturing and Controls	MAA	Marketing Authorisation Application
CPP	Certificate of Pharmaceutical Product	Mgt	Management
CTA(s)	Clinical Trial Application(s)		
DMF	Drug Master File	NeeS	Non-eCTD Electronic Submissions
FTIH	First Time In Human	PAC	Post Approval Commitment
eCTD	Electronic Common Technical Document	PIP	Paediatric Investigation Plan
EMA	European Medicines Agency	PM	Project Management
EU	European Union	PMF	Plasma Master File
GMP	Good Manufacturing Practice	PoC	Proof of Concept
IV	Intravenous	PV	Pharmacovigilance

Abbreviations (2)

QC	Quality Check/Control	SWOT	Strengths, Weaknesses, Opportunities, Threats
RA	Regulatory Affairs	TC(s)	Teleconference(s)
R&D	Research & Development	TOC	Table of Contents
ROW	Rest of World	TPP	Target Product Profile
RUT	Readability User Test	US	United States
SA	Scientific Advice	xTPP	X Traget Product Profile (X= Clinical or Quality or Critical)

Thank you very much for your attention!

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