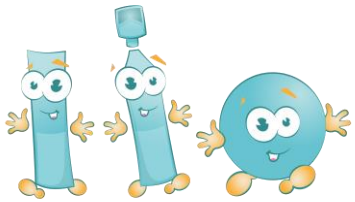


UNITHER PHARMACEUTICALS

SINGLE BEST WAY TO DELIVER

EMA/CHMP SCIENTIFIC ADVICE
ANALGESIC FIXED DOSE COMBINATION

BIOBRIDGES PRAGUE / 26-27th Sept. 2019

- Nathalie MASSON / Innovation & Development Director-

Sept. 26, 2019

UNITHER IN A NUTSHELL

CONTRACT DEVELOPMENT & MANUFACTURING ORGANIZATION

Focused on key pharmaceuticals niches

INDEPENDENT COMPANY

36% owned by management / 64% private equity funds

GROWING COMPANY

€286 million in 2018 and 1,332 employees

GLOBAL COMPANY

Industrial footprint in 3 continents

Products sold in more than 100 countries (USA / China / etc.)

WORLDWIDE LEADER ON BFS TECHNOLOGY

2.6 billion doses manufactured in 2018

NEW ODTECH® PLATFORM FOR READY-TO-USE ORAL FORMS

Liquid/Powder stick-packs, Orodispersible tablets, Buccal Trans-mucosal

GLOBAL ORGANIZATION

USA
Rochester, NY

BRAZIL
Barretos
Sao Paulo

FRANCE
Amiens
Bordeaux
Colomiers
Coutances
Gannat
Paris

CHINA
Wuhan

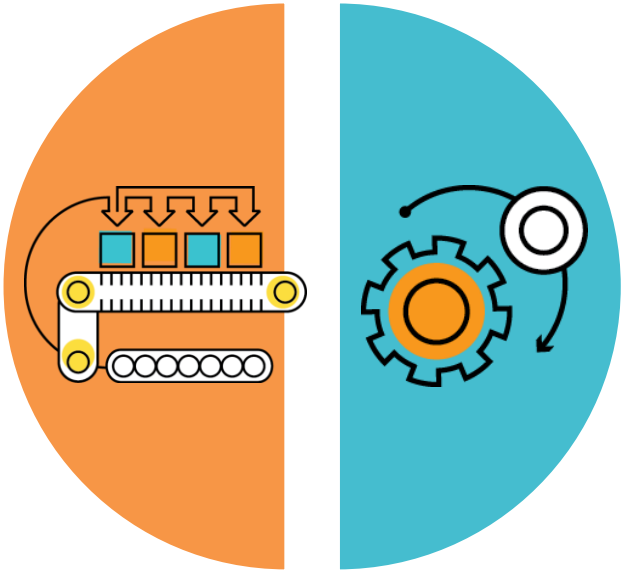
Production *Commercial Office* *Innovation & development*

UNITHER BUSINESS MODEL

Dual Business model

Contract Development & Manufacturing Organization

for strategic outsourcing |



Turn-key products & Dossiers

| for licensing in

NEW PRODUCT DEVELOPMENT CONTEXT

*for clinical development management only

DEVELOPMENT BY A SME

- **HC < 250 p.**
- **TO < 50 M€**

NON OPIOID ANALGESICS

- **Moderate to severe pain**
- **EMA/CHMP/970057/2011** Guideline on the clinical development of medicinal products intended for the treatment of pain

FIXED DOSE COMBINATION

- **2 already known APIs**
- **Oral route of administration**
- **EMA/CHMP/158268/2017** Guideline on clinical development of fixed combination medicinal products

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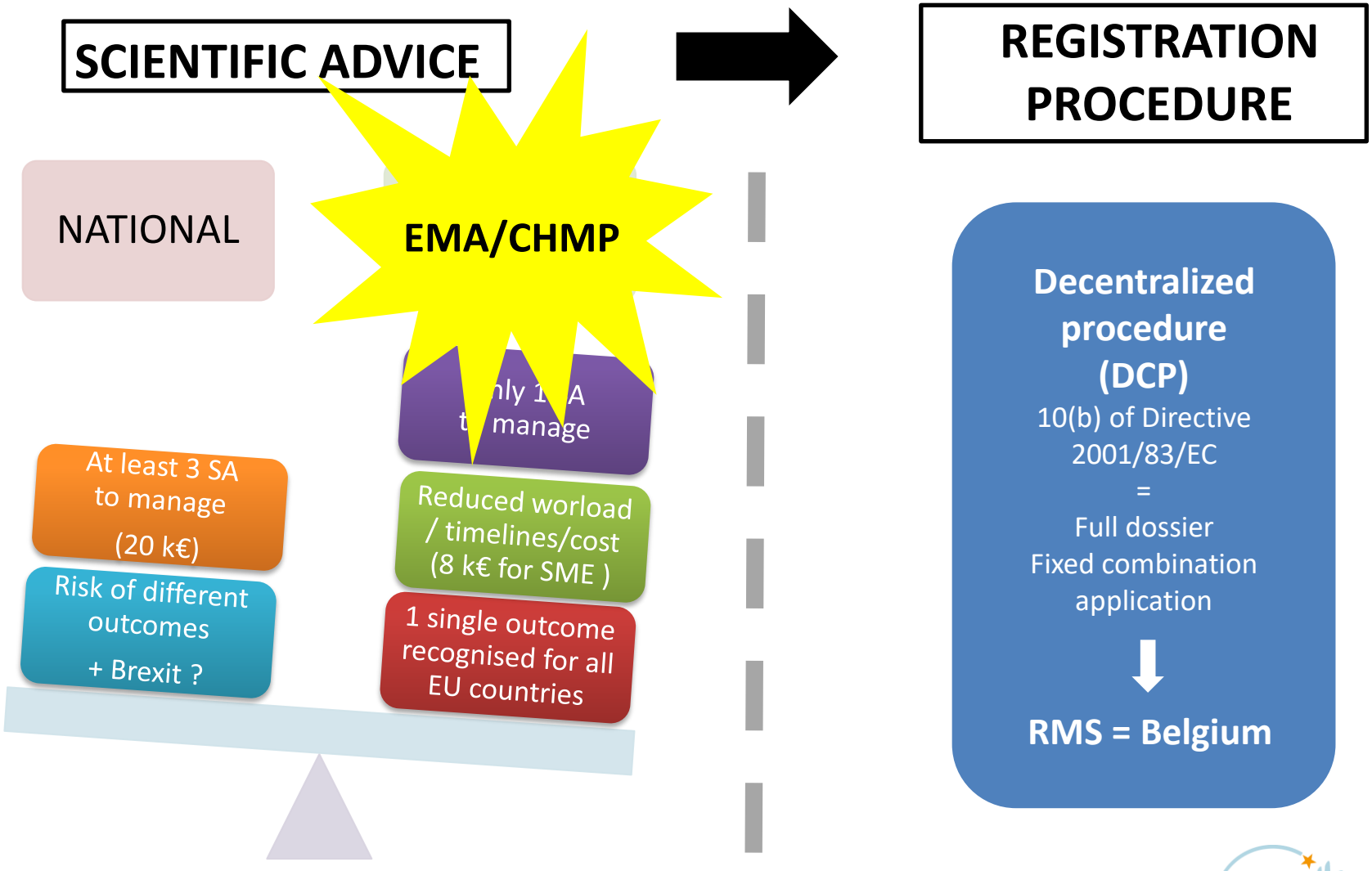
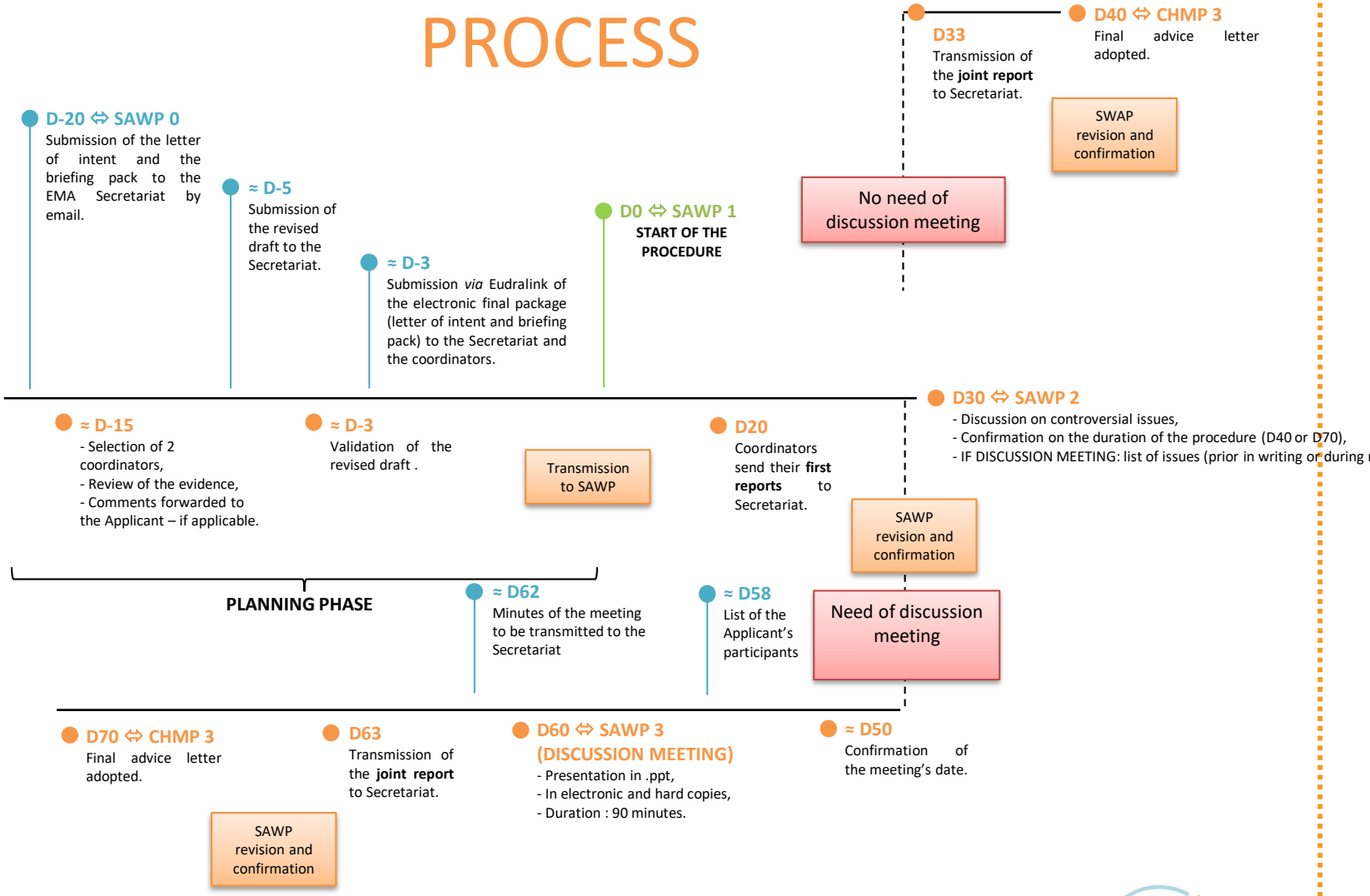
WHO PAIN LADDER

STEP 1 **Mild pain**	Optional adjuvant (NSAIDs including COX-2 inhibitor)	+	Non-opioid (such as paracetamol or aspirin)	-	-
If pain persists or increases, go to step 2					
STEP 2 **Moderate pain**	Optional adjuvant (NSAIDs including COX-2 inhibitor)	+	Non-opioid (such as paracetamol or aspirin)	+	Weak opioid (codeine, dihydrocodeine or tramadol)
If pain persists or increases, go to step 3					
STEP 3 **Severe pain**	Optional adjuvant (NSAIDs including COX-2 inhibitor)	+	Non-opioid (such as paracetamol or aspirin)	+	Strong opioid (morphine, diamorphine, fentanyl, buprenorphine, oxymorphine, oxycodone, or hydromorphone)
Freedom from pain					

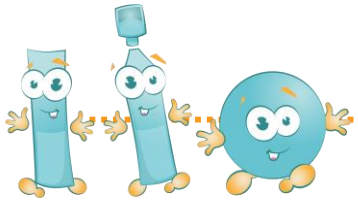
REGULATORY APPROACH



EMA/CHMP SCIENTIFIC ADVICE PROCESS



SCIENTIFIC ADVICE CONTENT



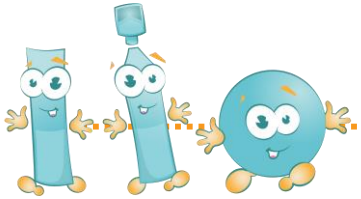
- **Objective**

  To receive feedback on the proposed development plan of the FDC in the treatment of moderate to severe pain and specifically on the proposed phase III clinical trial

- **EMA position requested on:**
  - acceptance that non-clinical studies are not required
  - acceptance on the proposed phase III study :
    - *study design*
    - *proposed baseline pain score*
    - *proposed primary and secondary endpoints*
    - *choice of statistical hypothesis*
    - *acceptance of the proposed rescue medication*
  - sufficiency of the proposed clinical studies and results to support the MAA
  - proposed indication and posology

Paediatric questions not included, subject to a separate advice (PDCO)

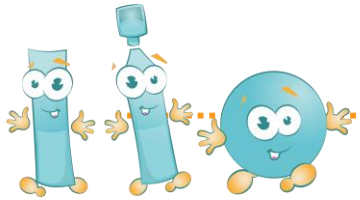
OUR FEEDBACK ON EMA/CHMP SCIENTIFIC ADVICE PROCESS



- Very clear process
- Defined calendar & timelines
- Easy submission through Eudralink
- Acknowledgement of receipt at each step
- Some clarifications requested in written
- Request to provide all literature references in English
- No discussion meeting needed
- Report received on time

No visible impact of EMA transfer from UK to NL !

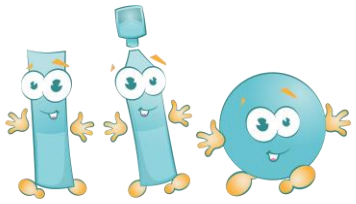
OUR FEEDBACK ON EMA/CHMP SCIENTIFIC ADVICE ANSWERS



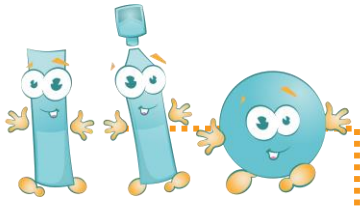
- **Positive comment on the product itself**
  - « CHMP agrees that there could be a place for this FDC »
- **Existing data on each API not sufficient to justify the FDC**
  - Dose/ratio to be further justified
  - Bridging toxicological package with FDC + ERA to be provided
- **Clear recommendations on toxicological studies to be performed**
- **Clinical phase III study**
  - Pain model, criteria of inclusion, end points, rescue : accepted
  - Study design challenged : control groups, comparators strength, duration
- **Clinical program to be extended with different pain models to obtain the full pain relief indication**
  - Extrapolation from one pain model (somatic) to other types of pain (visceral and chronic) not accepted, even if included in current RCPs

NEXT STEPS

- **Follow-up answers**
  - 1st set of answers (2019)
    - *Provide toxicological studies protocols as recommended*
    - *Provide additional arguments to better justify the proposed dose/ratio*
    - *Propose a revised tighter indication*
  - 2nd set of answers (2020)
    - *Provide revised phase III study design*
- **Implementation of all studies after endorsement by EMA/CHMP**



TAKE AWAY MESSAGES



- ✓ **Seek advice at the very beginning of the development of a new product**
  - -> don't wait for pharmaceutical development completion
  - -> some activities (tox.) can be anticipated and handled in parallel
- ✓ **Be careful with guidelines evolution**
- ✓ **Be transparent on what you plan to do and your rationale**
- ✓ **Take advantage of recommendations to ensure receivability of the final registration dossier (even if not binding)**
- ✓ **Define which Health Authorities you will approach for SA according to your product specificities**

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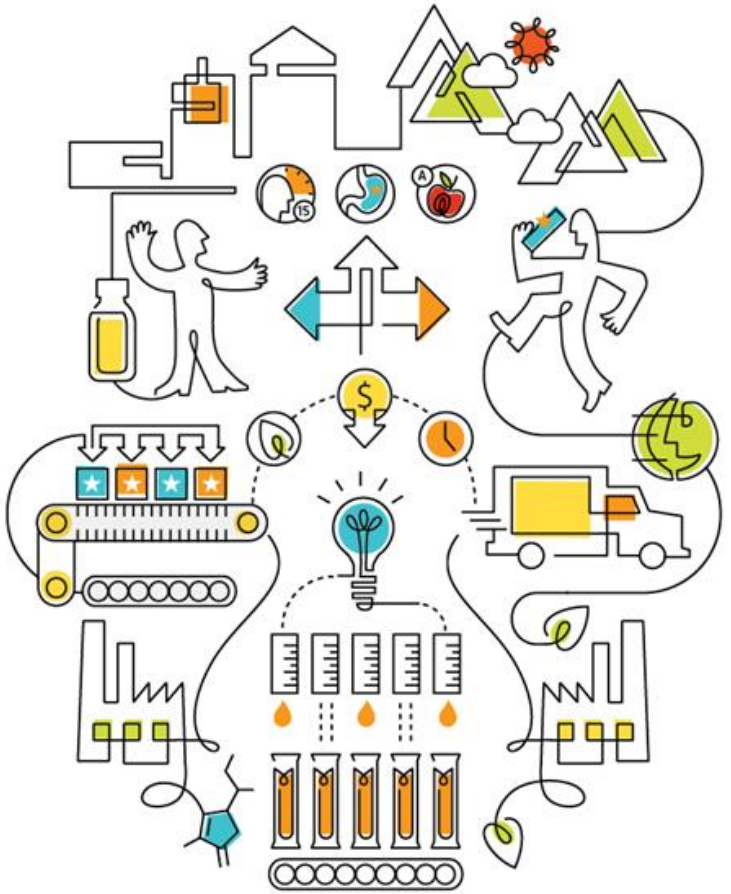
THANK YOU
FOR YOUR ATTENTION



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