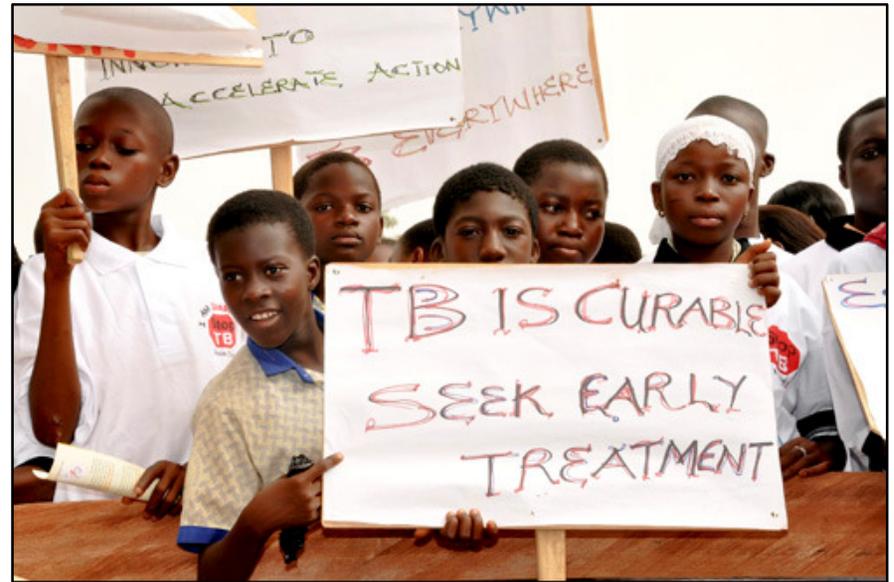


Updates on new policies including introduction of new drugs



2nd Meeting of the Core Group of the Global Drug-resistant TB Initiative

Barcelona, 27th Oct 2014

Christian Lienhardt
Global TB Programme
World Health Organization
Geneva, Switzerland

Overview of the presentation

- The WHO Strategic Plan for rational introduction of new TB drugs and regimens in countries
- The WHO Policy Implementation Package
- *A working example:* the rational Introduction of bedaquiline in countries
 - WHO Interim Policy Guidance on the use of bedaquiline
 - Work with Early Implementing Countries

Public health challenges of introduction of new TB drugs in countries

Implications for TB control programmes:

- Determine *optimal regimens* for treatment of DS- and DR-TB under programmatic conditions;
- evaluate requirements for patients' eligibility;
- assess programmatic feasibility;
- evaluate effectiveness and cost-effectiveness;
- ensure proper surveillance and pharmacovigilance – *especially if accelerated/conditional approval*;
- ensure *responsible use* (appropriate indication, doses, drug combination(s), and treatment duration) ;
- prevent emergence of resistance.

The WHO Strategic Plan for rational introduction of new TB drugs and regimens in countries

Key Principles:

- Need for combination regimen(s),
- Adaptation to largely variable country settings (health and NTP infrastructure, geography, demography, TB epidemiology, level of preparedness, etc.),
- Ensure equitable access to safe and quality-assured new drugs for all patients in needs,
- Link with measures to prevent misuse of the drugs,
- Multistage and pluri-partner process.

The WHO Strategic Plan for rational introduction of new TB drugs and regimens in countries

Describes key elements of a process aimed at:

- producing policy recommendations for the treatment of TB (all forms), according to progress made in the development of new drugs or combinations of drugs,
- and*
- assisting countries in the implementation of these recommendations

http://www.who.int/tb/new_drugs/en/index.html


World Health Organization



Introduction and rational use of new drugs and drug regimens for TB treatment

CURRENT SITUATION

- Much progress has been made in research and development of new drugs for tuberculosis (TB) over the last decade.
- A series of Phase II and III trials of shortened treatment of drug-susceptible (DS) TB including re-purposed drugs (e.g. fluoroquinolones) or new dosages of known drugs (e.g. rifamycin, rifapentine) are presently on-going, with earliest results expected in 2013.
- Novel drugs are being evaluated in Phase IIb and III trials, including two drugs that are being tested for the treatment of multidrug-resistant TB (MDR-TB) (bedaquiline and delamanid), with dossiers submitted to drug regulatory authorities. One of these (bedaquiline) has recently been granted licensure by the U.S. Food and Drug Administration under its accelerated approval procedure.
- Novel drug combinations for shortened treatment of DS and/or drug-resistant (DR) TB, including new or re-purposed drugs, are under investigation.

UNMET NEEDS

- People with drug-susceptible TB need shorter and simpler therapy;
- People with drug-resistant TB need a more efficacious, fully oral, shorter, less toxic and safer therapy;
- People living with HIV need TB drugs with no or low drug-drug interactions with antiretrovirals;
- People with latent TB infection need shorter and safer therapy;
- Children with TB need a more child-friendly treatment.

WHY THIS GUIDANCE?

The likely introduction of new drugs or drug regimens for the treatment of DS- or DR-TB will have a series of public health implications, particularly regarding:

- the responsible use of new drugs as part of set combination regimens for the treatment of DS- or DR-TB;
- the programmatic feasibility and cost-effectiveness of newly-developed treatments;
- the capacity to monitor scaled-up use of new drugs, and conduct surveillance of drug-resistance;
- the prevention of emergence of new drug resistance.

Global TB Drug Pipeline

Discovery	Preclinical Development		Clinical Development		
Lead Optimization	Preclinical Development	IND	Phase I	Phase II	Phase III
Chloroquinolone Dpt Inhibitors	C2226-45 DC-1576	872343 TSA-354		AC22047 Bedaquiline (TMC-207)	Delamanid (OPC-67683)
GyrB Inhibitors	Q381			Linezolid	Clarithromycin
RNAI Inhibitors	S2059			Novel Regimens*	Rifapentine
Leads Inhibitors	S0443			391-021	
MtDNA Inhibitors				819apentec	
Mycobacterial Glycine Inhibitors				5Q-309	
Protonamide Analogs				Sarcosyl (PNU-120403)	
Streptogramins					
Thiazolidine (II) complexes					
Streptogramins					
Translocase-I Inhibitors					


WORKING GROUP
 ON NEW TB DRUGS
 www.who.int/tb/new_drugs
 Updated: June 2012

WHO STRATEGIC ROADMAP:
Policy development for introduction of new TB drugs or regimens in countries

- In April 2012, the WHO Stop TB Department established a Task Force to advise and assist WHO in the process of the development of policy guidance on the rational introduction and use of new drugs or drug regimens for TB treatment. The aim is to improve access to quality TB care and to protect against the emergence of drug resistance.
- A strategic roadmap was then developed, with the support of the Task Force, to guide WHO's timely development of appropriate policy guidance on treatment of DS- or DR-TB and related rational introduction and use. The roadmap also includes WHO's role in supporting Member States in the roll-out of recommended new drugs within defined regimens in programmatic conditions.
- The WHO Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) endorsed this roadmap in June, 2012.

SEE REVERSE FOR THE ROADMAP STEPS

For more information please visit our website:
http://www.who.int/tb/new_drugs

The WHO Strategic Plan

5 steps:

1. Determination of the **type of evidence & data** to be required by WHO to recommend the use of new drug(s)/ regimen(s) for the treatment of TB, and production of **technical information notes**
2. Development of a "***Policy Development Framework***" to establish recommendation for the introduction of new TB drugs/regimens in countries
3. Series of **Expert consultations** to evaluate new TB drugs/regimens coming out of the pipeline and revise/update treatment guidelines as appropriate
4. Recommendations and **TA for introduction in countries**
5. Market introduction

Expert consultations

Series of Expert consultations to evaluate new TB drugs/regimens coming out of the pipeline and revise/update treatment guidelines as appropriate

Indicative:

- Bedaquiline (Jan 2013)
- Delamanid (April 2014)
- Role of Fluoroquinolones in MDR-TB treatment
- Shortened MDR-TB treatment
- Treatment of LTBI

Introduction in countries

- Country preparedness:
 - background information on Health system and NTP infrastructures, and on epidemiological data ("*know your epidemics*")
- Country support to enable access to new drugs
 - Strengthened capacity for **diagnosis** (incl. drug resistance), **treatment monitoring** & **pharmacovigilance**
 - Sustained system for **supply of QA drugs**
 - Discuss **control mechanisms/regulations** to prevent irresponsible use of drugs, particularly in the private sector
 - Develop "*Pilot projects*" for initial deployment of new drugs with **harmonised methods and surveillance**
 - **Community/patients'** representatives contribution
 - Strong **collaboration** between key stakeholders

Key issues for introduction of new TB drugs or regimens

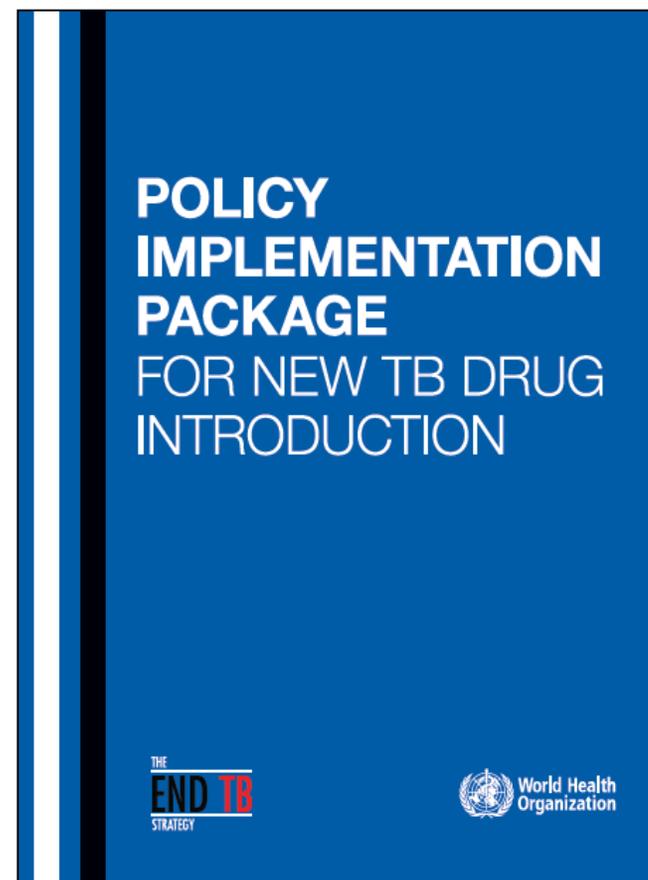
- *Main issues to address:*
 - delivery of - and access to treatment (by whom ? how ?)
 - risks to individuals (ADRs, DDIs) and implications
 - risk of irrational use (off-label, inadequate combinations, inadequate doses or duration, etc.)
 - risk for resistance development
 - feasibility and potential public health impact,
 - cost-effectiveness.

 - *great variability of national contexts (TB epidemics, health system and infrastructure, logistics, finance) !*

WHO Policy Implementation Package for Introduction of New TB Drugs or Drug Regimens in Countries

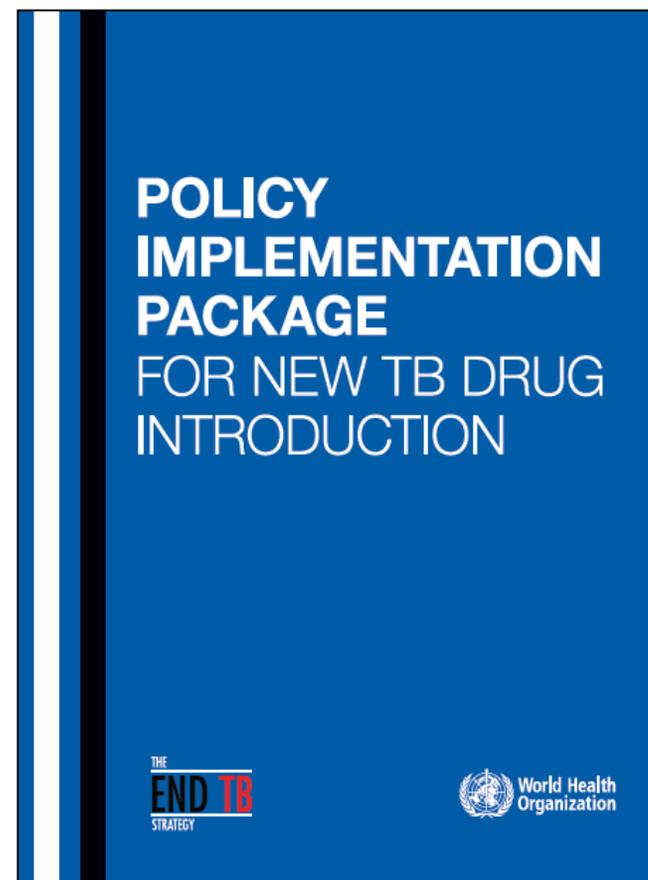
The goal of the **Policy Implementation Package** is to support countries in preparing for introduction of new TB drugs and/or regimens, based on WHO policy guidance, in order to better serve patients and communities in need.

WHO – Oct 2014



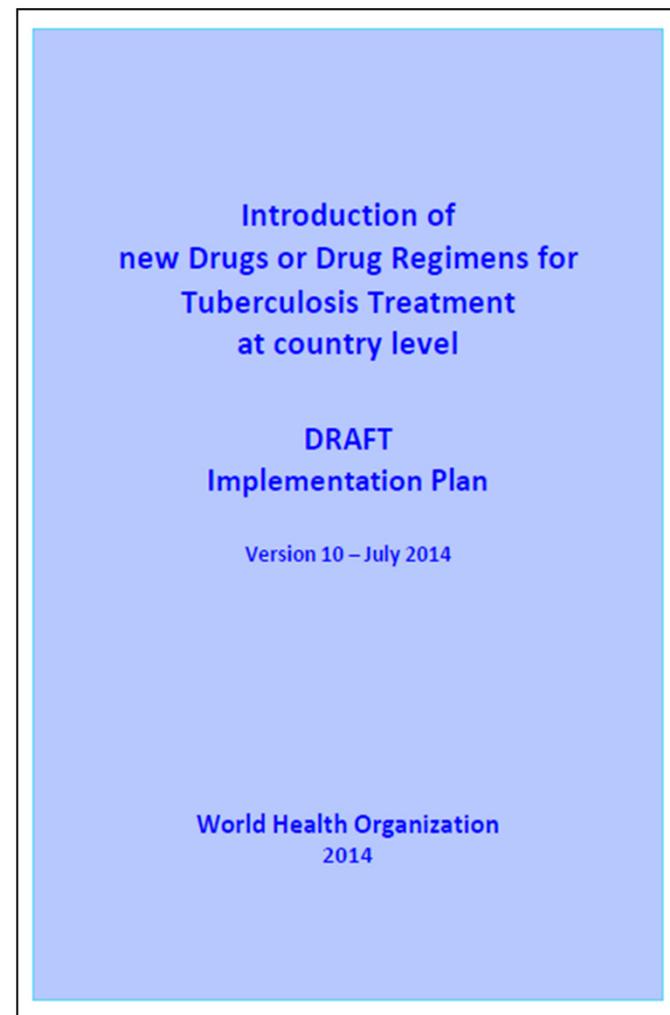
WHO Policy Implementation Package for Rational Introduction of New TB Drugs or Drug Regimens in Countries

1. **Minimum requirements** for country preparedness and planning.
2. **Implementation plan** for introduction of new TB drugs or regimens.
3. **Pharmacovigilance** and **drug resistance surveillance**.
4. **Private sector engagement**.
5. **Systems approach** for ensuring uninterrupted supply of quality-assured medicines .
6. **Operational research**



Generic Implementation Plan for Introduction of new TB Drugs or Drug Regimens in Countries

- Step 1: Establish the **framework** for the introduction of new drugs at country level
- Step 2: Meet the **minimal requirements** for introduction of new TB drugs
 - **checklist** for country readiness assessment
- Step 3: Develop a **national plan** for introduction of new TB drugs
- Step 4: Implement the introduction of new TB drugs in **pilot sites**
- Step 5: Generate evidence for **scale up**



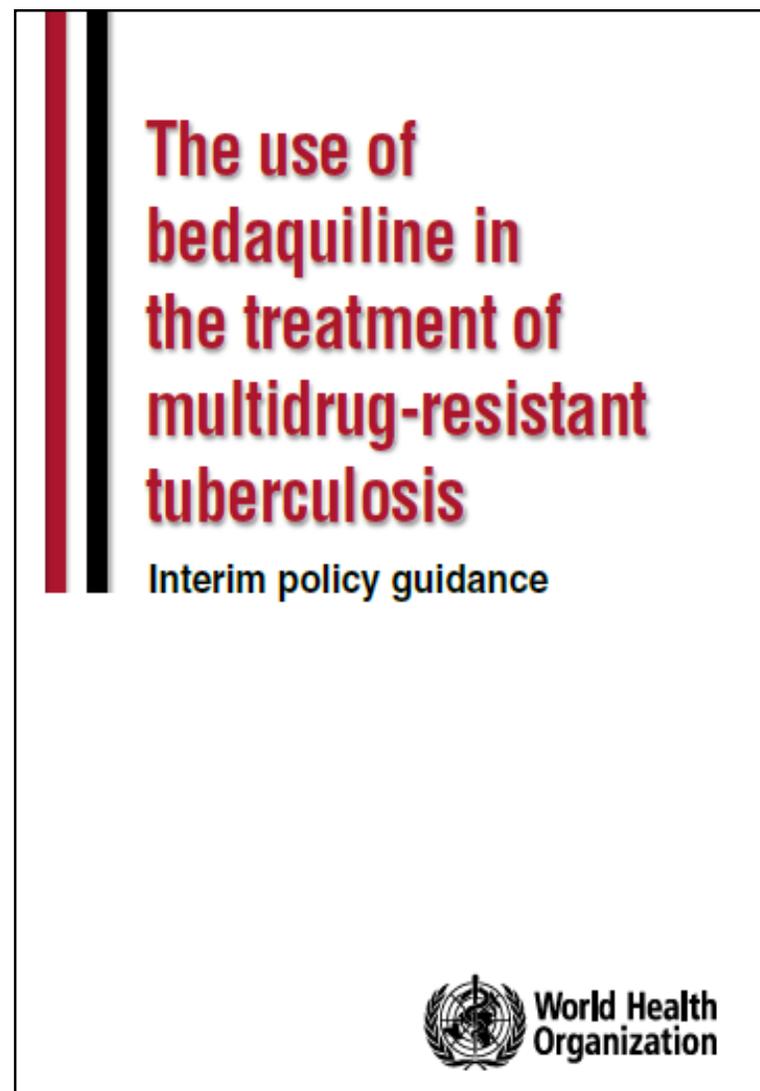
Interim policy guidance on the use of bedaquiline

"Bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB, under five specific conditions"

"conditional recommendation, very low confidence in estimates of effect"

http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf?ua=1.

WHO – June 2013



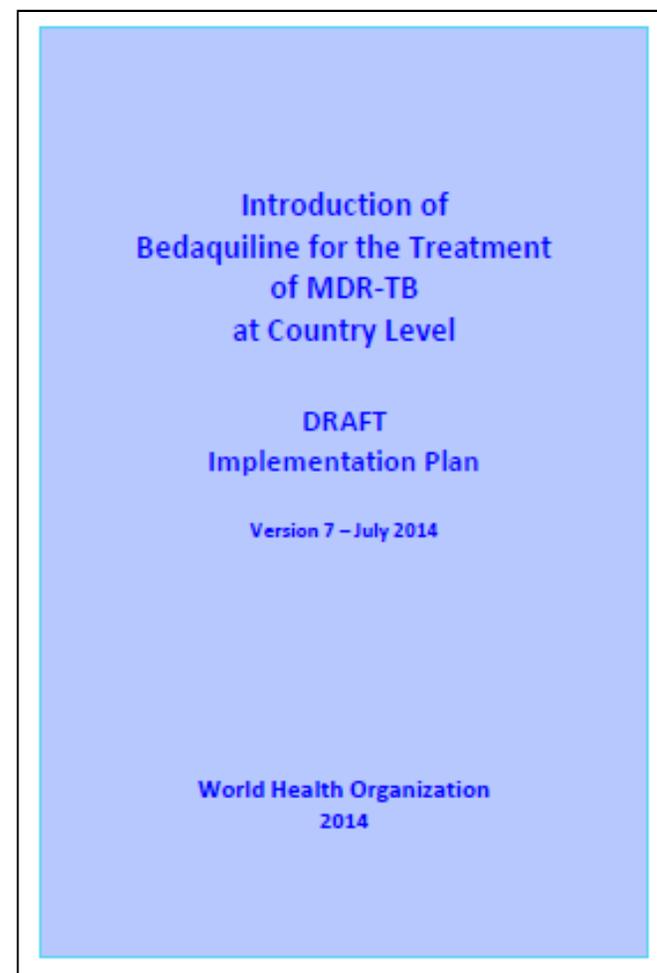
Interim policy guidance on the use of bedaquiline

5 conditions:

1. Proper selection of patients
2. Patient informed consent required
3. Treatment design based on WHO recommendations
4. Close monitoring conditions
5. Active pharmacovigilance and management of AEs

Implementation Plan for Introduction of Bedaquiline in Countries

- Step 1: Establish the framework for the introduction of bedaquiline at country level
- Step 2: Meet the minimal requirements for introduction of bedaquiline
 - *checklist* to assist in country preparedness
- Step 3: Develop a national plan for introduction of bedaquiline
- Step 4: Implement the introduction of bedaquiline in pilot sites
- Step 5: Generate evidence for scale up



Adapted with the assistance of Jennifer Furin (Feb – May 2014)

Work with early implementing countries

- A group of countries have expressed interest in working with WHO for *introduction of bedaquiline in programme conditions, following WHO recommendations*
- Vietnam, Philippines, Indonesia, Kazakhstan, Belarus

Work with early implementing countries

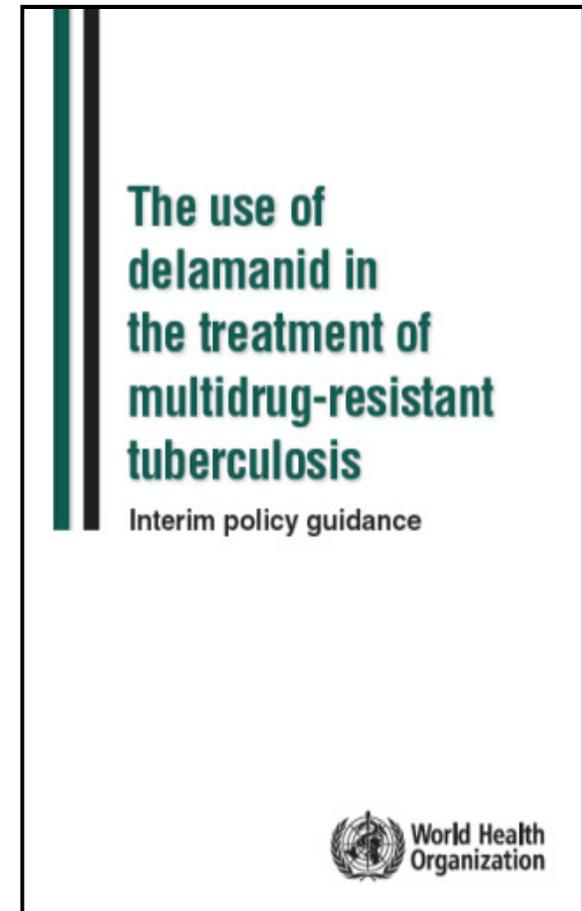
- Initial workshop involving all key stakeholders (NTP, MoH, NRA, NPV, etc.) and TA bodies/donors (GF, USAID, B&MGF, KNKV, etc..)
 - Outline of National Implementation Plan
 - Establishment of national framework
 - Identification of pilot sites
 - Determination of target cohort
 - Laboratory aspects
 - Monitoring – including recording and reporting
 - Establishment of active PV in conjunction with key stakeholders
 - Discussion with NRAs on import/regulatory aspects/drug procurement
 - Timeline of activities

Interim policy guidance on the use of delamanid

"Delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB, under five specific conditions"

"conditional recommendation, very low confidence in estimates of effect"

WHO – Oct 2014



Key messages

Key aspects for WHO/GTB are :

- to engage with and support national authorities and stakeholders early in the preparation of policies for introduction of new TB medicines at programmatic level (including quality, procurement aspects, etc.);
- to ensure that new TB medicines/regimens are introduced in an optimal way to protect patients from misuse and prevent emergence of resistance;
- to ensure that introduction of new medicines follows policy recommendations and appropriate plans are made to ensure feasibility and inform policy-making.

Acknowledgements

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*Thank you for
your attention !*

