ANVISA
New Regulatory Framework for APIs

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Overview

RDC 359/2020

- Primarily intended for DIFA holders
- DIFA
- DIFA holder
- CADIFA
- Submission procedure
- API-related changes
- Suspension/Withdrawal

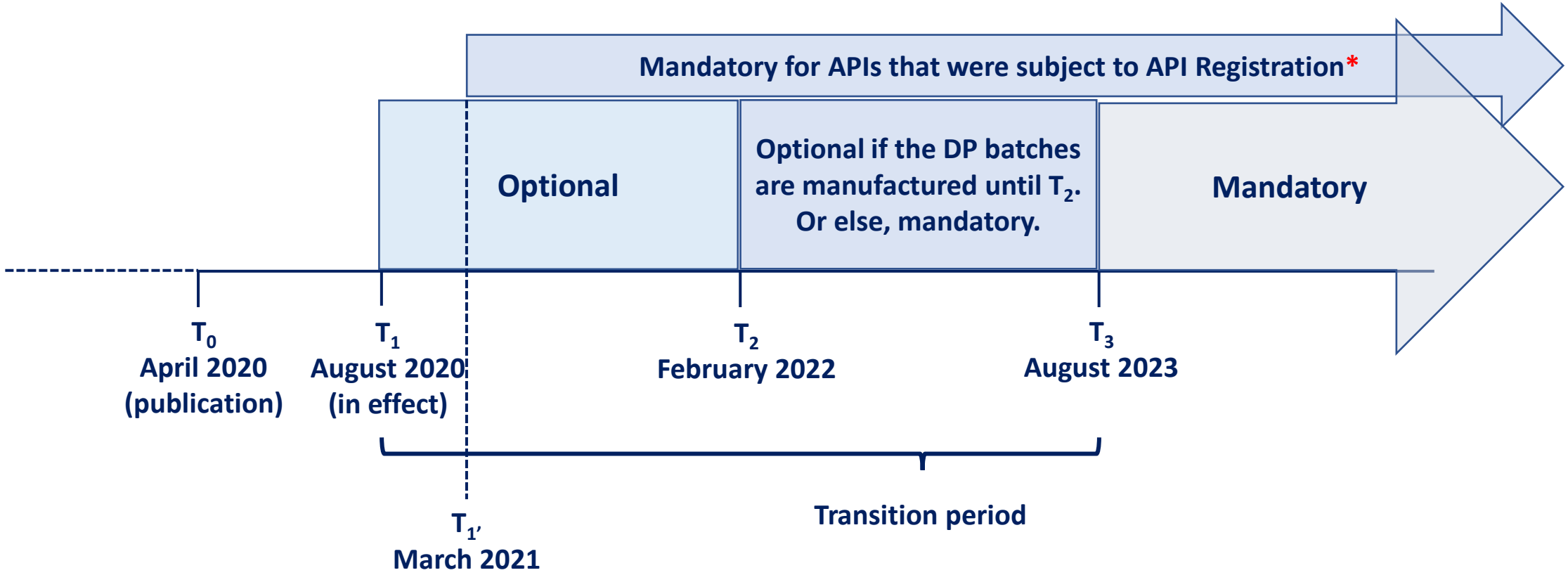
RDC 361/2020

- Primarily intended for MA applicants/holders
- Alters:
  - RDC 200/2017 (marketing authorisation applications)
  - RDC 73/2016 (variations to marketing authorisations)

RDC 362/2020

- Defines the criteria for GMP certification of foreign API manufacturers

Timeline



*APIs listed in IN 15/2009 & IN 3/2013

Main aspects

1. Centralised assessment
2. Single Resolution for APIs (RDC 359/2020)
3. Direct communication with DIFA holders (Brazilian or foreign)
4. International harmonization through adoption of ICH guidelines (*pertaining to APIs*)
5. Mandatory audit conducted by the Marketing Authorisation Holder/Applicant (RDC 301/2019 & RDC 361/2020)
6. GMP Certification/Inspections (RDC 362/2020)

Centralised assessment / Single Resolution

Before & Transition period	New Policy
MA applications DP + API (RDC 200/2017)	**MA applications** DP (RDC 200/2017)
Variations to MAs DP + API (RDC 73/2016)	**Variations to MAs** DP (RDC 73/2016)
API Registration Specific lists RDC 57/2009	**API** **RDC 359/2020**
! **Multiple API-related guidelines**	! **Fully centralised assessment of APIs**

Initial submission

I. Associated CADIFA application:

   a. With confidentiality restrictions;

   b. No confidentiality restrictions;

II. Standalone CADIFA application:

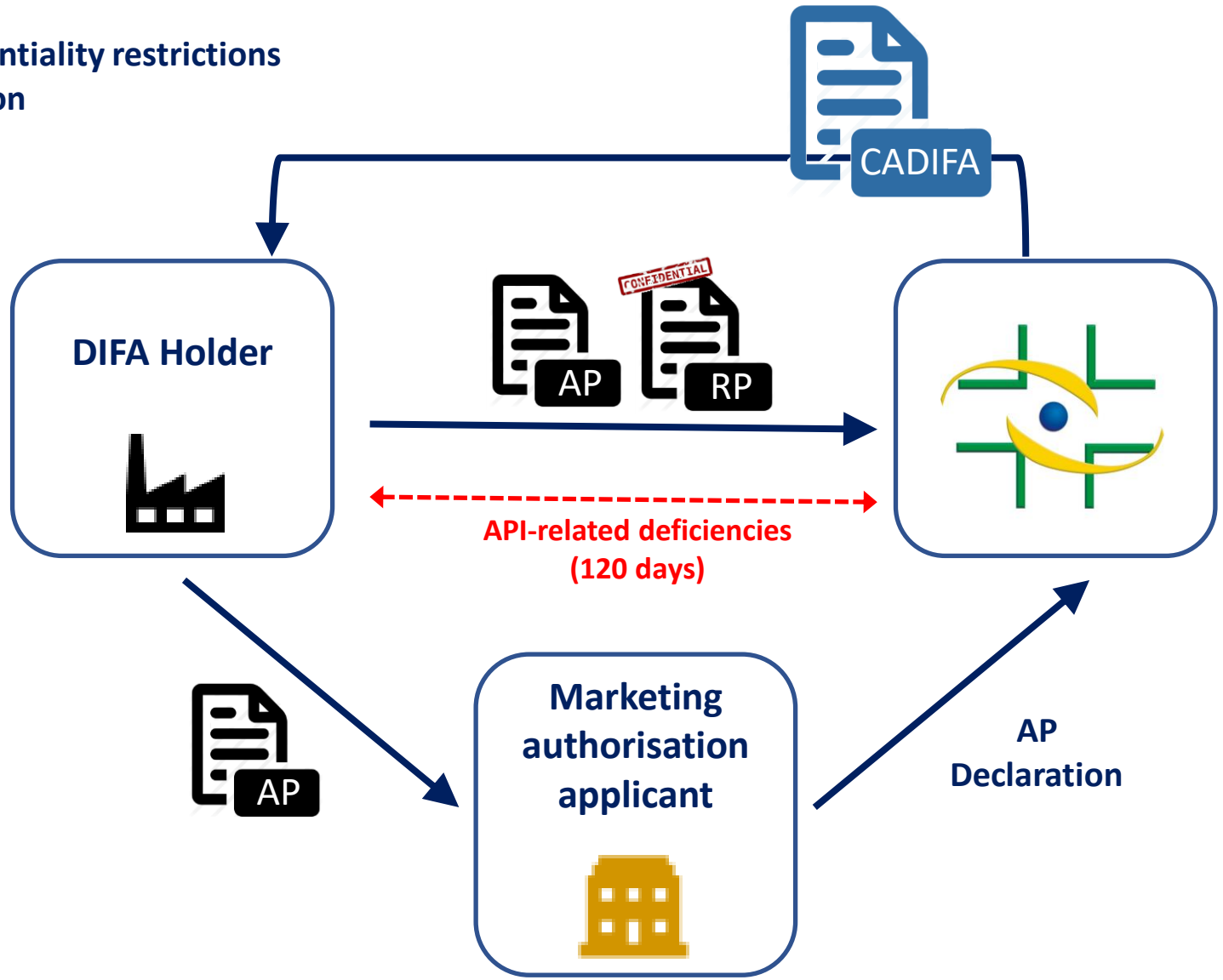
   c. Expression of interest from manufacturers;

   d. Public invitation issued by the BoD (ANVISA).

Submission procedure

Example 1:

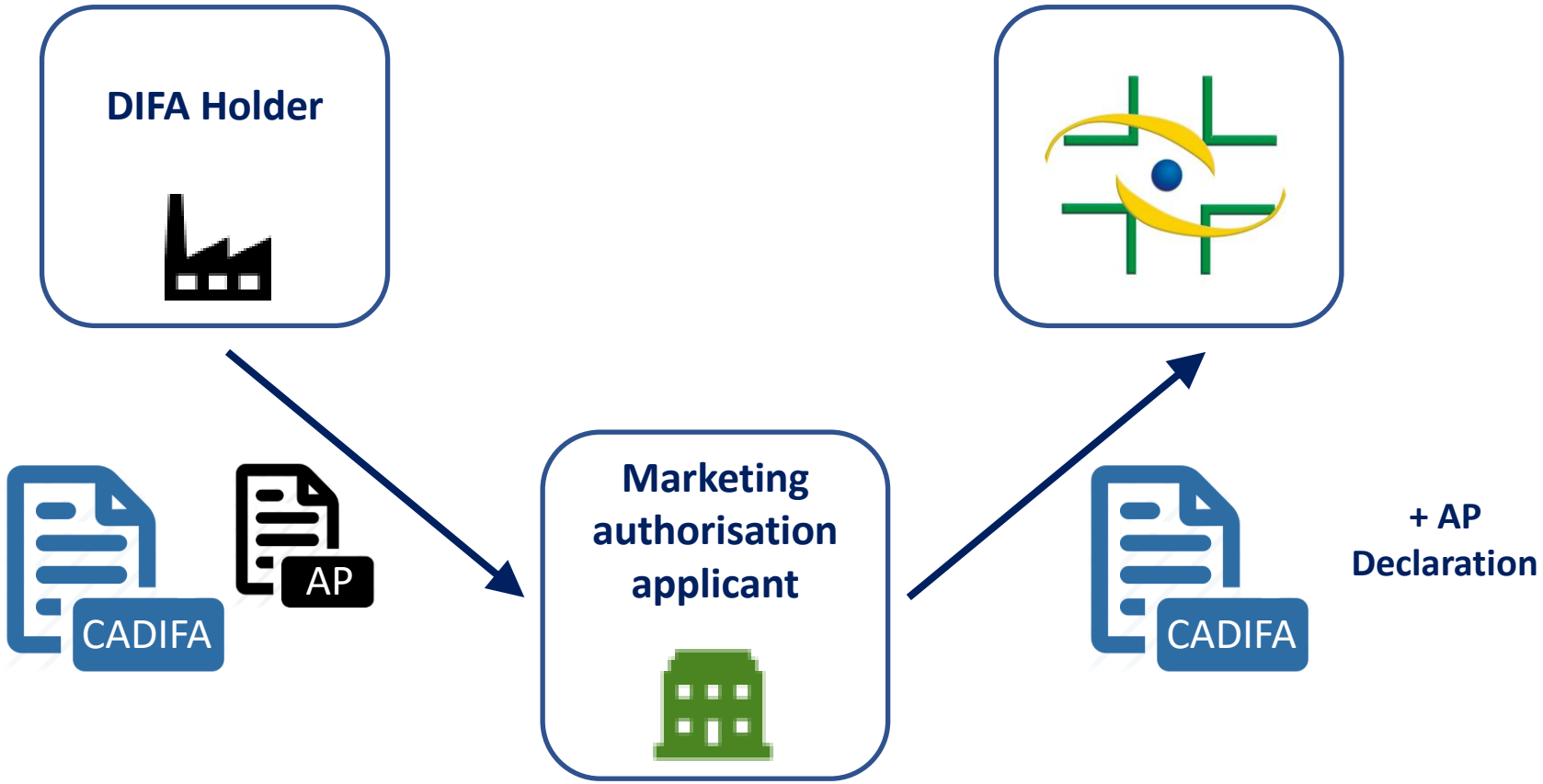
- **With confidentiality restrictions**
- **1st submission**



Submission procedure

Example 2:

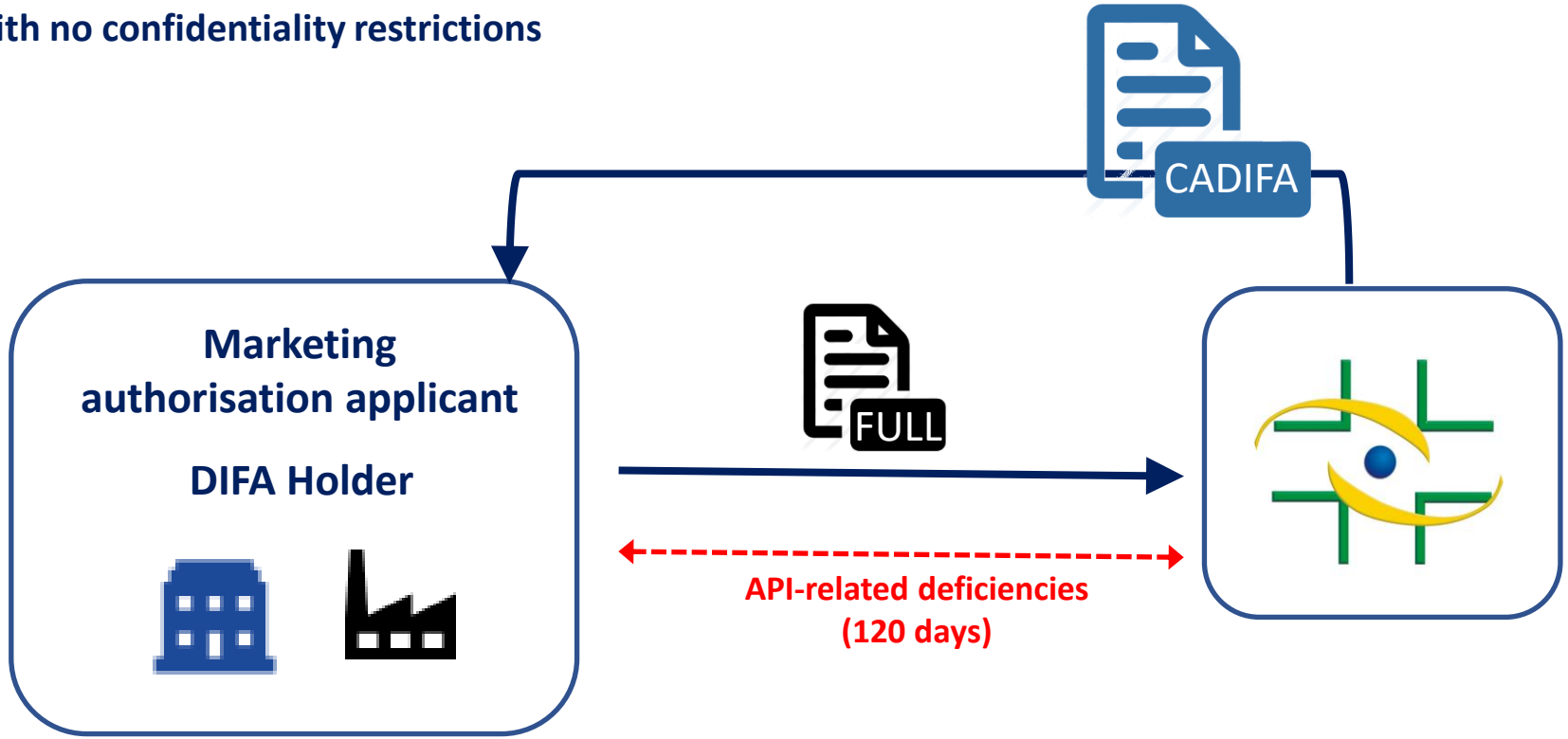
- **With confidentiality restrictions**
- **2nd/3rd […] submissions**



DIFA - Submission procedure

Example 3:

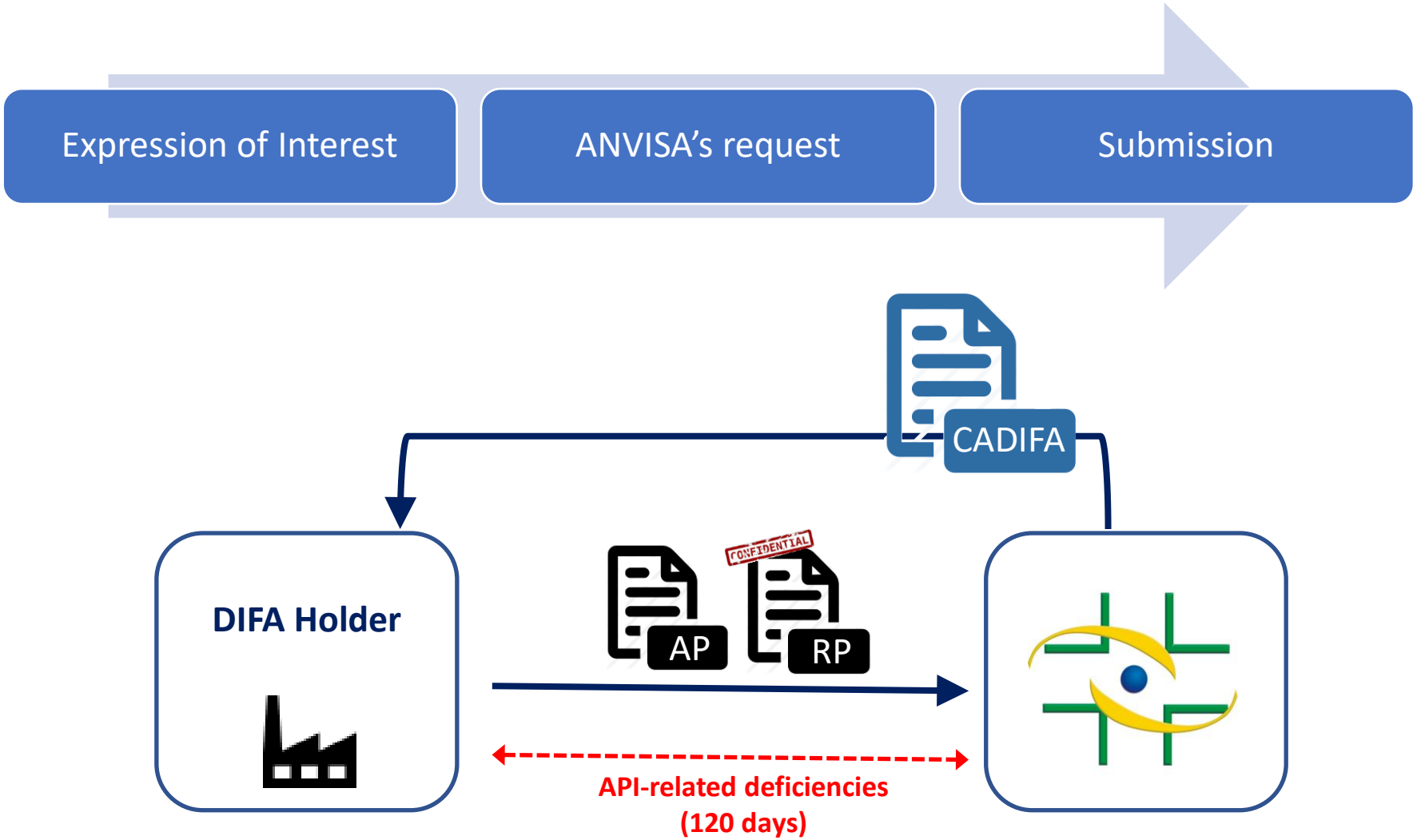
- **With no confidentiality restrictions**



DIFA - Submission procedure

Example 4:

- **Expression of interest**



API-Related Changes

RDC 359 – Annex II

1 - Mudanças Administrativas

1.1 Mudança na razão social e/ou designação do endereço do detentor da CADIFA	Condições	Documentos	Tipo de alteração
	1	1, 2	Notificação imediata
Condições			
1. A entidade legal detentora da CADIFA deve ser mantida (exceto nos casos de venda ou fusão da empresa).			
Documentos			
1. Documento formal de um órgão oficial em que a nova razão social e/ou novo endereço são mencionados. 2. Declarações dos incisos III e IV do art. 12 desta Resolução atualizadas.			

1.2 Mudança da razão social e/ou designação do endereço de local de fabricação ou controle de qualidade do IFA	Condições	Documentos	Tipo de alteração
	1	1	Notificação imediata
Condições			
1. O local de fabricação ou controle de qualidade deve permanecer o mesmo.			
Documentos			
1. Documento formal de um órgão oficial em que a nova razão social e/ou novo endereço são mencionados.			

1.3 Mudança da razão social e/ou designação do endereço do fabricante do material de partida utilizado na fabricação do IFA	Condições	Documentos	Tipo de alteração
	1	1	Notificação anual
Condições			
1. O local de fabricação deve permanecer o mesmo.			
Documentação			
1. Lista atualizada (com razão social e endereço completos) de fabricantes de material de partida aprovados e propostos.			

1.4 Mudança da razão social e/ou designação do endereço do fabricante de intermediário utilizado na fabricação do IFA	Condições	Documentos	Tipo de alteração
	1	1	Notificação imediata
Condições			
1. O local de fabricação deve permanecer o mesmo.			
Documentos			
1. Lista atualizada (com razão social e endereço completos) de fabricantes de intermediários aprovados e propostos.			

1.5 Exclusão de local de fabricação de intermediário ou de local de fabricação ou controle de qualidade do IFA	Condições	Documentos	Tipo de alteração
	1	1, 2	Notificação imediata
Condições			

EDQM (revision CEPs)

4.I. ADMINISTRATIVE CHANGES

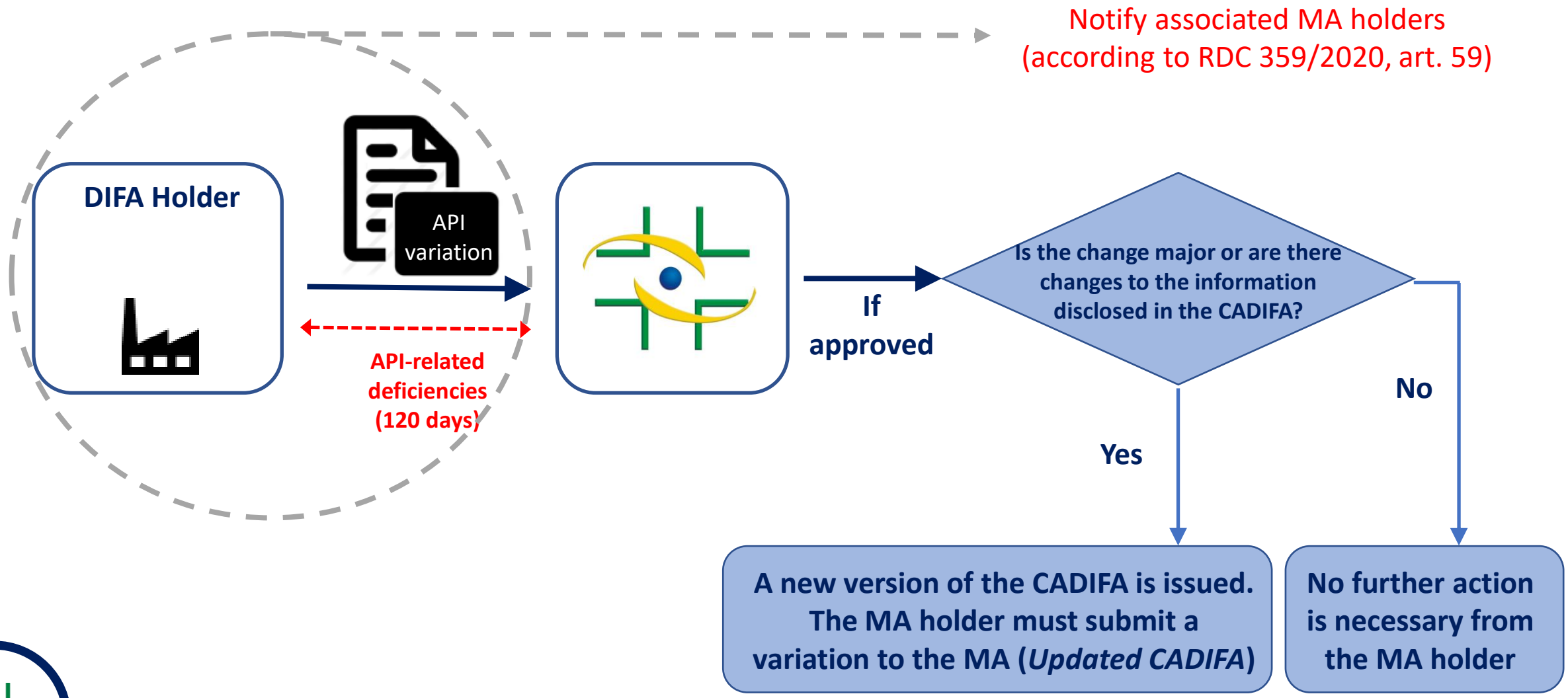
This type of changes applies to chemical, double, herbal and TSE certificates of suitability.

4.I.1 Change in the name and/or address of the certificate holder	Conditions	Specific documentation	Type of change
	1	1, 2	IN
Conditions			
1. The certificate holder must remain the same legal entity (exception to this condition: where the company is sold or in the event of a company merger).			
Documentation			
1. A formal document from a relevant official body in which the new name and/or new address is mentioned.			
2. All updated declarations (annexes to the application form).			

4.I.2 Change in the name and/or address of a manufacturing site or a quality control testing site for the final substance	Conditions	Specific documentation	Type of change
	1	1, 2, 3	IN
Conditions			
1. The location of the manufacturing site or the quality control site must remain the same.			
Documentation			
1. A formal document from a relevant official body in which the new name and/or address is mentioned.			
2. Updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected (annexes to the application form).			
3. If needed, updated annexes to the CEP reflecting the change of name.			

4.I.3 Change in the name and/or address of a manufacturer of a starting material used in the manufacture of the final substance	Conditions	Specific documentation	Type of change
	1	1	AN
Conditions			
1.The location of the manufacturing site must remain the same.			
Documentation			
1. Updated list (with name and complete address) of approved and proposed manufacturers of starting material.			

Change application



CADIFA

CADIFA

I. Number and issue date.

II. API, DCB, CAS.

III. Name and address of DIFA Holder.

IV. Name and address of manufacturing sites.

V. API Specification and, if applicable, compendial reference.

VI. Container closure system.

VII. Storage conditions.

VIII. Retest period or shelf-life.

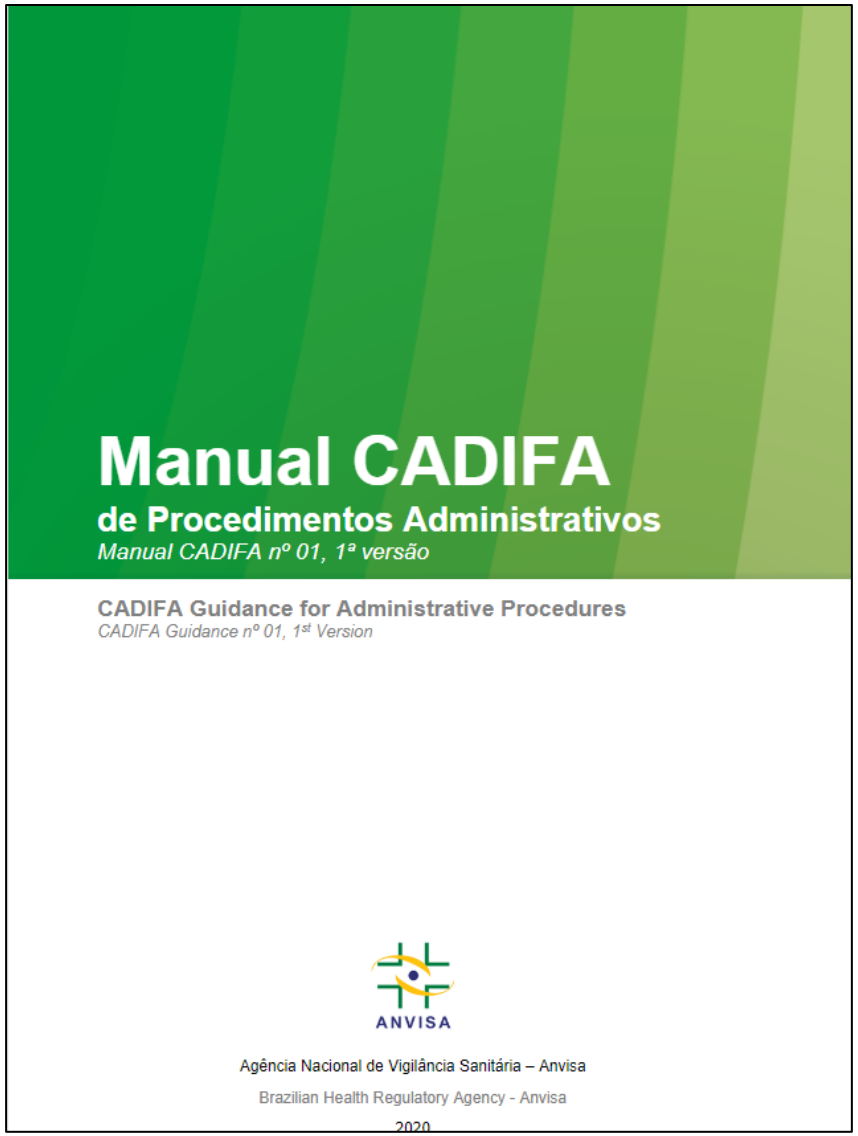
IX. Declaration of access.

Administrative procedures – Submission format

- DIFA holders will use ANVISA Submission Systems
- Electronic submission (non-eCTD)
  - Module 1 + Module 2 (optional) + Module 3
- Non-electronic submission
  - Guia 24/2019 (ICH M4)
  - Module 1 + Module 2 + Module 3

Administrative procedures – CADIFA Guidance

- Initial submission
- Change application
- Response
- Additional information
- Closure
- Suspension (by DIFA holder)
- Closure (by DIFA holder)



LINK

Adoption of ICH guidelines (*pertaining to APIs*)

- ICH M4Q (3.2.S)
- ICH Q1_
- ICH Q2
- ICH Q3A
- ICH Q3C
- ICH Q3D (*RDC 359/2019 - Annex I*)
  - With RMS
  - No RMS
- ICH Q6A
- ICH Q11
- ICH M7

CADIFA - Suspension & Withdrawal

- Documental and/or GMP related issues.
- Severity of the issue and recurrence will determine whether a CADIFA will be suspended or withdrawn by ANVISA.
- A MA application associated with a suspended/withdrawn CADIFA will preclude the MA from being granted
- Measures of interest to public health regarding the API and the drug products associated with a suspended/withdrawn CADIFA might be undertaken (e.g. suspension of importation or manufacture).
- A CADIFA may also be suspended or withdrawn by its holder.

RDC 362/2020 - GMP

- Risk assessment-based inspections programme
- No change regarding GMP requirements (RDC 69/2014, ICH Q7)
- Scope: foreign API manufacturers.
- A GMP Certificate of the API manufacturer issued by ANVISA will be a requirement for a marketing authorisation or addition of API manufacturer (RDC 361/2020).

GMP - RDC /

- **The GMP Certificate will be issued in one of three ways:**

Inspection conducted by ANVISA

Risk assessment
+
Inspection conducted by an authority recognised as equivalent by ANVISA

Risk assessment

RDC 318/2019

- **Long term stability (for room temperature):**

Storage condition	Stability condition
Room temperature (between 15°C e 30°C)	30°C±2°C/75%RH±5%RH
	30°C±2°C/70%RH±5%RH
	30°C±2°C/65%RH±5%RH
Room temperature (between 15°C e 25°C)	25°C±2°C/60%RH±5%RH

- **Forced degradation and photostability are a requirement**

COIFA (API Department) website

https://www20.anvisa.gov.br/coifaeng/

http://portal.anvisa.gov.br/english/api

TO BE UPDATED...

Thank you for your attention!

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