Metformin premix: challenges encountered during reclassification from co-processed API use to resolve severe metformin agglomeration to pharmaceutical intermediate

M-CERSI Workshop Co-Processed API

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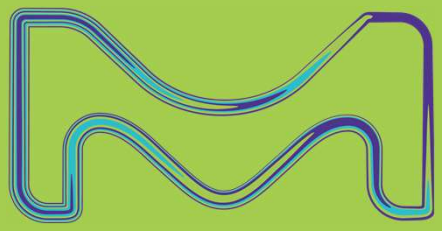


EMD Serono MilliporeSigma EMD Electronics

Agenda

AS ONE for patients

01 Background

02 Metformin Premix reclassification

03 Storyline

04 Main challenges encountered

05 Main impacts identified

06 Benefits

Metformin Premix (Co-Processed API)

Background: Why was metformin premix developed?

1

Glucophage® (API Metformin Hydrochloride) was first **approved in 1959** as immediate release tablet for first-line medication for the treatment of type 2 diabetes.

2

Metformin Hydrochloride **tends to form large and hard agglomerates** when stored in drums, making it difficult to work with for the manufacture of the drug product.

3

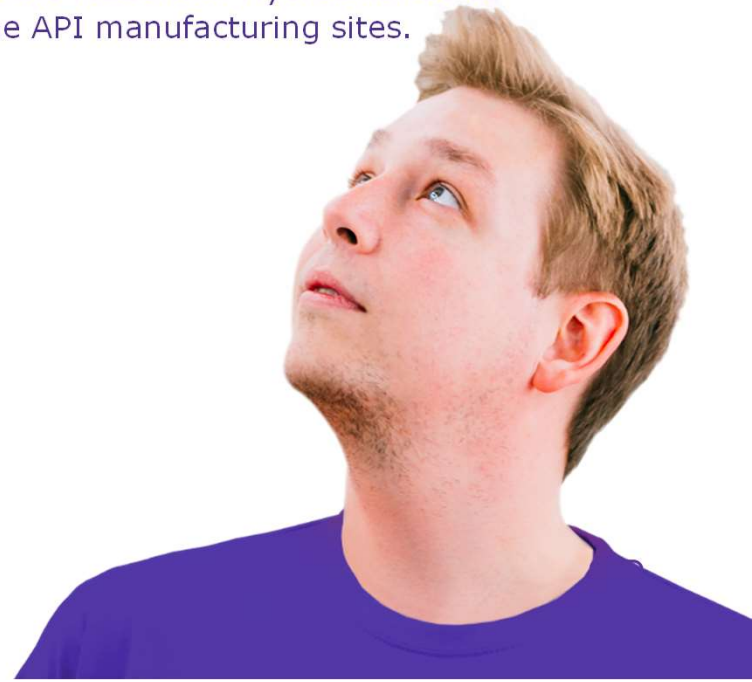
To **improve powder flowability**, an anticaking premix was developed in 1995, with addition of 0.5 % of magnesium stearate to the Metformin Hydrochloride at the API manufacturing sites.

4

Magnesium Stearate was selected because it is an excipient already used in the drug product formulation.

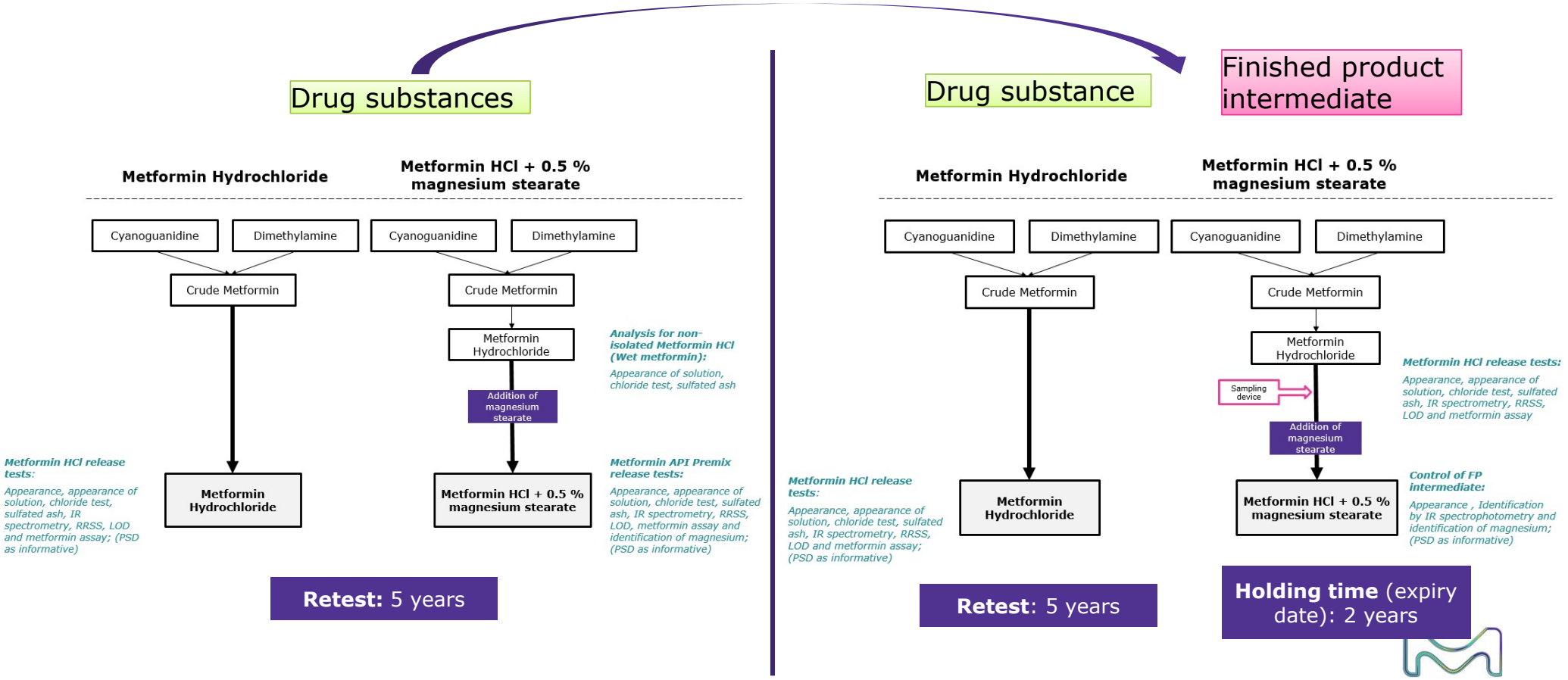
5

Metformin premix was **registered as drug substance** in 1999 in the quality part of the dossier for Glucophage ®, in 2001 for Glucovance® (FDC Metformin and Glibenclamide) and in 2004 for Glucophage® XR.



Metformin Premix

Same product, "only" reclassification from Drug Substance to Pharmaceutical intermediate



Metformin Premix as Pharmaceutical Intermediate
Storyline

2010

Pharmaceutical GMP certificate in place for API manufacturing sites

Since 2010, following a request from a customer (limited to the powder blending) due to new registration

2016

Project kicked off

Cross-functional team set up; regulatory strategy defined for Wave 1 (EU countries)

2021

Metformin premix as pharmaceutical intermediate first submissions and approvals

Approval received for Glucophage® and Glucophage® XR in EU; escalated implementation following grace periods

2016

EMA Q&A on API mix was issued

"A justification based only on workability reasons (e.g., to ease handling when processed into final dosage form) is not acceptable" → not challenged by us

2020

Change in GMP Certificate at first API manufacturing site

Metformin Hydrochloride + 0.5 % Magnesium stearate removed by ANSM (French HA) from our GMP certificate for active substance

2022…and beyond

Metformin premix as pharmaceutical intermediate roll out

Regulatory strategy defined in waves for Glucovance®, EU followers and international countries; related activities ongoing

End of the project? At least 4 More years

Project completed by

≈15%

(nr of registered countries)

Metformin Premix as Pharmaceutical Intermediate

Main challenges encountered (so far) during the journey

Regulatory

- **Glucophage®** (500/850/1000 mg), **Glucophage® XR** (500/750/850/1000 mg) and **Glucovance®** (250/1.25; 500/2.5; 1000/5; 500/5 mg); are **marketed in >130 countries** → Extremely complex environment with changing and challenging regulatory strategy set up → huge effort
- Module 3 from DS part to DP part; **chemical sites registered as DS site and DP site** (2 GMP certificates needed: 1 for Drug Substance (API) and 1 for Premix as Pharmaceutical Intermediate) → x 2 audits
- **Lack of GMP certificate** at API manufacturing sites for metformin premix as API could impact countries/customers still having premix as API consideration

Technical

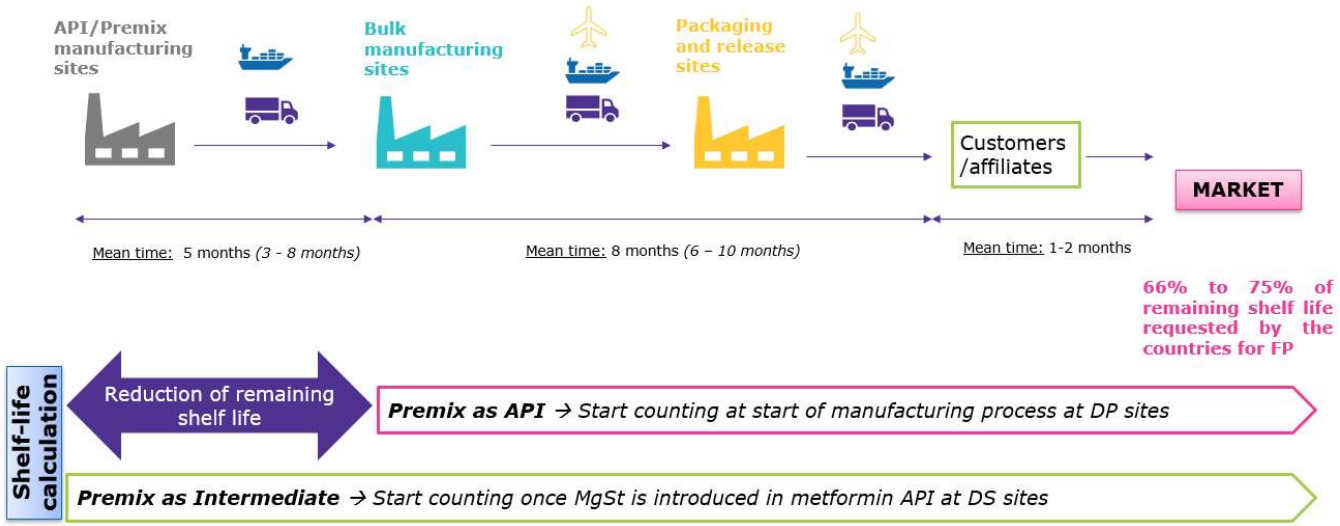
- About **3 years** for installation and qualification of sampling device on each Metformin production line to sample Metformin API before entering the blender. Main issues faced:
  - Clogging
  - Crusting
  - Lack of sample representativity
  - Sample contamination
  - Cleaning process

Metformin Premix as Pharmaceutical Intermediate

Main (negative) impacts identified because of reclassification *(1/2)*

On Product (both Metformin premix and Drug Product)

- **Reduction of remaining shelf life** → Extension of the DP SL to compensate the new way to calculate expiry date



- Metformin premix 5 years retest (as DS) vs 24 months holding time (as intermediate) → **Supply impact**
- Reassessment of bulk holding times and **supply impact on bulk deliveries**
- Need for **transport validation** of metformin premix (all routes).

Metformin Premix as Pharmaceutical Intermediate

Main (negative) impacts identified because of reclassification *(2/2)*

On Manufacturing sites

- **For implementation:**
  - **Significant resources** are dedicated at manufacturing sites (both chemical and pharma sites) as per huge workload due to implementation of premix as intermediate → Double code creation, quality systems modification, SAP and LIMS configuration, grace period management,…
  - **Complexity significantly increased** (number of SKUs)

- **In routine:**
  - **Quality audits and/or GMP inspection** at chemical sites **doubled** (API + pharmaceutical intermediate)
  - **Release time** for premix pharmaceutical intermediate **increased by 10%** due to additional test per batch
  - **Cost increase** → Reprocessing not accepted in premix pharma intermediate

Metformin Premix as Pharmaceutical Intermediate

Benefits? What is gained by the reclassification as pharmaceutical intermediate?

Is there any advantage that may be identified from:

- **Patient** perspective?
- **Quality** perspective?
- **Regulatory** perspective?
- **Process** perspective?