CÔNG TY CP DƯỢC LIỆU TRUNG ƯƠNG 2	CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM
	Độc lập – Tự do – Hạnh phúc
Số: 4058 /DL2-TBV	*TP. Hồ Chí Minh ngày 19 tháng 8 năm 2024*
V/v: Thông báo thay đổi màu sắc và thành phần vỏ nang Lipanthyl 200M	

Kính gửi: - SỞ Y TẾ TỈNH NINH THUẬN
- TRUNG TÂM Y TẾ THÀNH PHỐ PHAN RANG-THÁP CHÀM

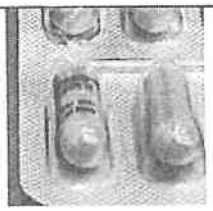
Trước tiên, Công ty Cổ phần Dược Liệu Trung Ương 2 xin cám ơn sự hỗ trợ và hợp tác của Quý Khách hàng đối với công ty chúng tôi. Trong nhiều năm liền, các sản phẩm của công ty chúng tôi đã được Quý Khách hàng tin tưởng và sử dụng để điều trị cho bệnh nhân.

Căn cứ Quyết định số 08/QĐ-SYT ngày 05/01/2024 của Giám đốc Sở Y Tế Ninh Thuận về việc phê duyệt kết quả lựa chọn nhà thầu Gói số 01: Gói thầu Thuốc Generic và vắc xin năm 2023.

Công ty chúng tôi đã trúng thầu và đang cung ứng đến Quý khách hàng sản phẩm **Lipanthyl 200M** *(Fenofibrate 200mg; dạng bào chế: viên nang cứng)*, **số đăng ký VN-17205-13** của nhà sản xuất **Astrea Fontaine**, chi tiết như sau:

Mã hàng	Tên thương mại	Hoạt chất-Nồng độ - Hàm lượng	Dạng bào chế-Đường dùng	Quy cách đóng gói	SĐK hoặc GPNK	Cơ sở sản xuất-Nước sản xuất	Đơn vị tính	Số lượng trúng thầu và phân bổ
G10525	Lipanthyl 200M	Fenofibrat-200mg	Viên nang cứng-Uống	Hộp 2 vỉ x 15 viên	VN-17205-13	Recipharm Fontaine-Pháp	Viên	10.000

Chúng tôi trân trọng thông báo có sự thay đổi trong màu sắc và hình thức viên nang như sau:

Viên nang đang lưu hành	Viên nang sẽ thay đổi
 Viên nang màu cam và có chữ "Lipanthyl 200M", "Sản xuất tại Pháp"	 Viên nang màu cam đất và không có chữ

Nội dung thay đổi trên đã được Cục quản lý dược phê duyệt ngày 28/6/2023 công văn số 6852/QLD-ĐK cho phép thay đổi tiêu chuẩn chất lượng dược chất, thay đổi qui trình sản xuất thuốc, thay đổi màu sắc và thành phần vỏ nang, cập nhật phương pháp phân tích tiêu chuẩn chất lượng thuốc.

nngthanh

Thay đổi này không ảnh hưởng chất lượng thuốc, thay đổi này sẽ được áp dụng cho các lô hàng được nhập khẩu về Việt Nam trong tháng 8/2024. Tuy nhiên trong giai đoạn chuyển giao sẽ có sản phẩm với cả hai hình thức viên nang được lưu hành trên thị trường.

Công ty chân thành cảm ơn sự hợp tác của Quý khách hàng.

Trân trọng kính chào./.

TL. TỔNG GIÁM ĐỐC

M.S.D.N: 0302597576 - C.T.C.P * CÔNG TY CỔ PHẦN DƯỢC LIỆU TRUNG ƯƠNG 2 * QUẬN 1 - T.P HỒ CHÍ MINH

GIÁM ĐỐC DỰ ÁN THẦU BỆNH VIỆN
Hoàng Văn Phúc

Nơi nhận:
- *Như trên;*
- *Lưu VT,TBV*

Tài liệu đính kèm:
1. Công văn 6852/QLD-ĐK

576 - C.T.C.P * TY ẦN LIỆU ƯƠNG 2 HỒ CHÍ MINH

nngthanh

Lipanthyl

BỘ Y TẾ
CỤC QUẢN LÝ DƯỢC

Số: 6852 /QLD-ĐK
V/v thay đổi TCCL dược chất, thay đổi QTSX thuốc, thay đổi màu sắc và thành phần vỏ nang, cập nhật PPPT tiêu chuẩn chất lượng thuốc

CỘNG HOÀ XÃ HỘI CHỦ NGHĨA VIỆT NAM
Độc lập - Tự do - Hạnh phúc

Hà Nội, ngày 28 tháng 6 năm 2023

Kính gửi: Abbott Laboratories (Singapore) Private Limited
Địa chỉ: 3 Fraser street, #23-28 DUO Tower, Singapore 189352.
Văn phòng đại diện: Tầng 7, tòa nhà Handi-Resco, 521 Kim Mã, quận Ba Đình, Hà Nội.

Cục Quản lý Dược nhận được hồ sơ số tiếp nhận 858/TĐNN ngày 16/05/2022 và các tài liệu liên quan của Công ty về việc thay đổi tiêu chuẩn chất lượng dược chất, thay đổi quy trình sản xuất thuốc, thay đổi màu sắc và thành phần vỏ nang, cập nhật phương pháp phân tích tiêu chuẩn chất lượng thuốc đối với thuốc đã được cấp giấy đăng ký lưu hành.

Căn cứ Thông tư số 08/2022/TT-BYT ngày 05/09/2022 của Bộ trưởng Bộ Y tế quy định việc đăng ký lưu hành thuốc, nguyên liệu làm thuốc.

Căn cứ Biên bản thẩm định hồ sơ thay đổi/ bổ sung của công ty, Cục Quản lý Dược có ý kiến như sau:

Đồng ý về việc thay đổi tiêu chuẩn chất lượng dược chất, thay đổi quy trình sản xuất thuốc, thay đổi màu sắc và thành phần vỏ nang, cập nhật phương pháp phân tích tiêu chuẩn chất lượng thuốc đối với thuốc Lipanthyl 200M, số đăng ký: VN-17205-13, cụ thể như sau:

Bảng so sánh nội dung thay đổi được đóng dấu xác nhận của Cục Quản lý Dược và đính kèm theo công văn này.

Ngoài nội dung được thay đổi trên, tất cả các nội dung khác giữ nguyên như hồ sơ đăng ký thuốc lưu tại Cục Quản lý Dược.

Cơ sở đăng ký, cơ sở sản xuất phải chịu trách nhiệm về chất lượng đối với thuốc lưu hành trên thị trường và có trách nhiệm thông báo sự thay đổi này đến các cơ quan liên quan và khách hàng.

Sau 12 tháng kể từ ngày ký công văn này, thuốc trên không được nhập khẩu với các nội dung cũ đã đề nghị thay đổi.

Cục Quản lý Dược thông báo để Công ty biết và thực hiện đúng các quy định của Việt Nam về lưu hành thuốc./.

Nơi nhận:
- Như trên;
- Cục trưởng (để b/c);
- Viện KN thuốc TƯ (để p/h);
- Viện KN thuốc TP HCM (để p/h);
- Lưu: VT, ĐKT (TTQ) (2b).

KT. CỤC TRƯỞNG
PHÓ CỤC TRƯỞNG

Nguyễn Thành Lâm

Table 1: Comparison of the CTD sections of pre-change and post-change dossiers

<table>
<tr><th>CTD Section</th><th>Pre-change</th><th>Post-change</th><th>Summary of the change</th><th>Reason for the change</th></tr>
<tr><td>3.2.S.2.1</td><td>Corden Pharma Chenove 47 Rue de Longvic 21300 Chenove, France — Manufacturing, testing, release</td><td>Corden Pharma Chenove 47 Rue de Longvic 21300 Chenove, France — Manufacturing, micronisation, testing, release</td><td>Micronization step added by drug substance manufacturer</td><td rowspan="3">Change in the manufacturing process from co-micronized to micronized fenofibrate in finished product manufacturing process.</td></tr>
<tr><td>3.2.S.4.1</td><td><table><tr><th>Test</th><th>Acceptance criteria</th><th>Analytical procedure</th></tr><tr><td>Particle size, in µm
- D90</td><td>
≤ 400 µm
≤ 630 µm</td><td>SOLID 1000160279</td></tr></table></td><td><table><tr><th>Test</th><th>Acceptance criteria</th><th>Analytical procedure</th></tr><tr><td>Particle size, in µm
D50
- D90
- D99</td><td>
≤ 15 µm
≤ 25 µm
≤ 50 µm</td><td>RTM.P1306</td></tr></table></td><td>PSD limits has been updated</td></tr>
<tr><td>3.2.S.4.2</td><td>SOLID 1000160279 - Particle size is determined on sieves of mesh 630 µm and 400 µm.</td><td>RTM.P1306 – Particle Size Determination by Laser Diffraction for Fenofibrate Micronized</td></tr>
</table>

BỘ Y TẾ
CỤC QUẢN LÝ DƯỢC
ĐÃ PHÊ DUYỆT
TĐ/BS ngày 28 tháng 6 năm 2023
(theo công văn 6852/QLD-ĐK)

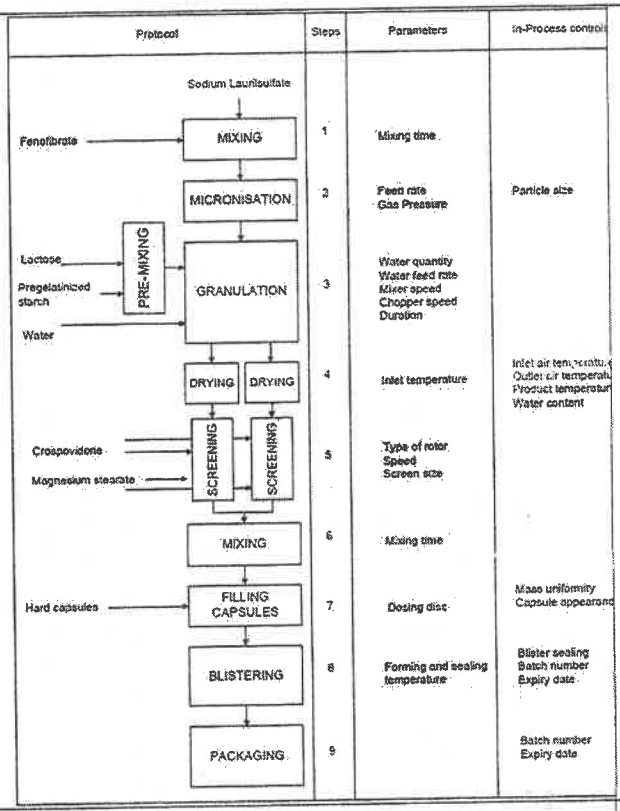
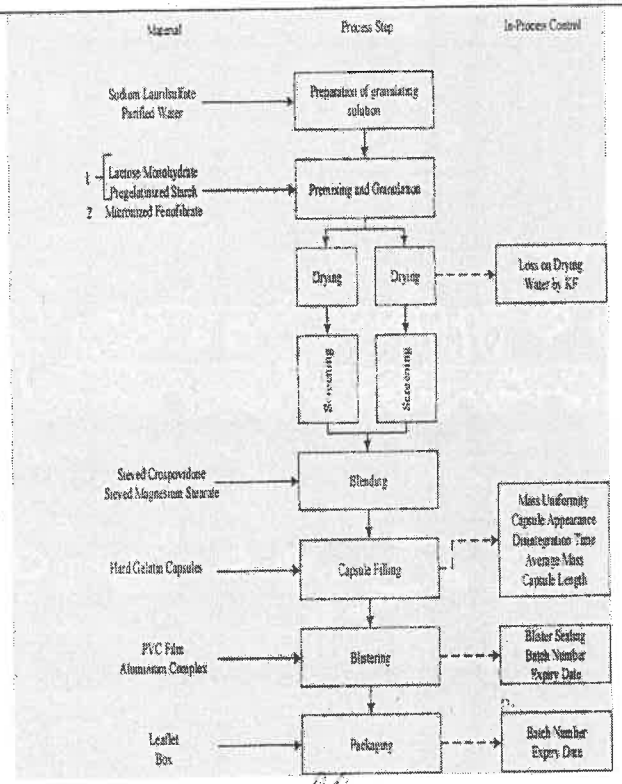
Fenofibrate Capsules 200mg – FP Mfg process change & Capsule Color Change- Minor Variation

<table>
<tr><th>CTD Section</th><th>Pre-change</th><th>Post-change</th><th>Summary of the change</th><th>Reason for the change</th></tr>
<tr><td>3.2.P.1</td><td>
Description of the dosage form
Opaque, orange capsule size 1, containing a white or almost white powder.

Composition of the Capsule Shell
<table>
<tr><th>Component</th><th>Theoretical quantity per capsule</th><th>Function</th><th>Reference</th></tr>
<tr><td>Titanium dioxide (E 171)</td><td>2.33%</td><td>Opacifier</td><td>Ph. Eur. (0150)[1] conforms to 95/45/EC</td></tr>
<tr><td>Iron oxide (E172)</td><td>1.50%</td><td>Coloring agent</td><td>conforms to 95/45/EC</td></tr>
<tr><td>Erythrosin (E127)</td><td>0.17%</td><td>Coloring agent</td><td>conforms to 95/45/EC</td></tr>
<tr><td>Gelatin</td><td>qs ad 100.0%</td><td>Filler</td><td>Ph. Eur. (0330)Error! Reference source not found.</td></tr>
</table>
[1] Current edition
</td><td>
Description of the dosage form
Opaque, ochre capsule size 1, containing a whitish powder.

Composition of the Capsule Shell
<table>
<tr><th>Component</th><th>Theoretical quantity per capsule</th><th>Function</th><th>Reference</th></tr>
<tr><td>Titanium dioxide (E 171)</td><td>1.00%</td><td>Opacifier</td><td>Ph. Eur.[1] conforms to (EU) 231/2012</td></tr>
<tr><td>Red iron oxide (E 172)</td><td>0.13%</td><td>Coloring agent</td><td>conforms to (EU) 231/2012</td></tr>
<tr><td>Yellow iron oxide (E 172)</td><td>0.70%</td><td>Coloring agent</td><td>conforms to (EU) 231/2012</td></tr>
<tr><td>Gelatin</td><td>qs ad 100.0%</td><td>Filler</td><td>Ph. Eur.[1]</td></tr>
</table>
[1] Current edition
</td><td>Change in the capsule color and composition. Update of the current references. Update of the description of the powder in the capsule.</td><td>The color of the capsules have been changed do to the removal off erythrosin, as this compound is considered that this compound in high doses could be potentially toxic. The change in the capsule color/composition has not impact of the drug product quality. The description of the dosage form is harmonized.</td></tr>
<tr><td>3.2.P.3.1</td><td>
<table>
<tr><th>Site</th><th>Function(s)</th></tr>
<tr><td>Corden Pharma Chenove 47 Rue de Longvic 21300 Chenove, France</td><td>Co-micronisation</td></tr>
<tr><td>Jet Pharma SA Via Sotto Bisio 42/A CP 234 – CH-6828 Balerna Switzerland</td><td>Co-micronisation</td></tr>
<tr><td>Recipharm Fontaine Rue Des Pres Potets 21121 Fontaine les Dijon, France</td><td>Manufacturing, packaging, testing, release</td></tr>
</table>
</td><td>
<table>
<tr><th>Site</th><th>Function(s)</th></tr>
<tr><td>Recipharm Fontaine Rue Des Pres Potets 21121 Fontaine les Dijon, France</td><td>Manufacturing, packaging, testing, release</td></tr>
</table>
</td><td>Removed Corden Pharma and Jet Pharma as co-micronisation sites</td><td>Sites removed as the API is directly purchased as micronized API. No comicronisation step is involved.</td></tr>
</table>

3.2.P.3.2	Component	Quantity	Reference	Component	Quantity	Reference	Fenofibrate has been changed to Micronized Fenofibrate. Number of capsules per batch has been changed from 982,200 to 982,114	The API for the manufacturing has been changed from Comicronisate (SLS+Fenofibrate) to micronised Fenofibrate. Based on the batch size of the final blend, the number of capsules has been revised to 982,114 capsules.
	Fenofibrate	202.3 kg	Ph. Eur. (1322)[1]	Micronized Fenofibrate	202.3 kg[1]	Ph. Eur.[2]		
	Sodium laurilsulfate	7.1 kg	Ph. Eur. (0098)[1]	Sodium laurilsulfate	7.1 kg[1]	Ph. Eur. [2]		
	Lactose monohydrate	99.2 kg	Ph. Eur. (0187)[1]	Lactose monohydrate	99.2 kg	Ph. Eur. [2]		
	Pregelatinised starch	29.46 kg	Ph. Eur. (1267)[1]	Pregelatinised starch	29.46 kg	Ph. Eur. [2]		
	Crospovidone	6.87 kg	Ph. Eur. (0892)[1]	Crospovidone	6.87 kg	Ph. Eur. [2]		
	Magnesium stearate	4.91 kg	Ph. Eur. (0229)[1]	Magnesium stearate	4.91 kg	Ph. Eur.[2]		
	Purified water[2]	qs granulation	Ph. Eur. (0008)[1]	Purified water[2]	qs granulation	Ph. Eur.[2]		
	Size 1 capsules	≈ 982,200	In-house	Size 1 capsules	≈ 982,114	In-house		
	[1] Current edition [2] Used for granulation, removed during manufacture The manufacturing formula presents an overage of 3% in fenofibrate/sodium laurilsulfate comicronisate, calculated on the theoretical weight of comicronisate (196.4 kg fenofibrate + 6.9 kg sodium laurilsulfate). This formula corresponds to the amounts of products used for the production of one batch of finished product. Mixing and comicronisation of fenofibrate with sodium laurilsulfate are performed on batches using 414.0 kg of fenofibrate. A part of these batches of intermediate product, 209.4 kg, is used to produce one batch of finished product.			[1] This quantity includes an overage of 3%. [2] Current edition [3] Used for granulation, removed during manufacture				

3.2.P.3.3.1			Process starts with preparation of granulating solution. Micronised Fenofibrate is mixed with the lactose and pregelatinized starch for granulation	Revised the flow diagram as per the new manufacturing process with micronized API.
3.2.P.3.3.2	Step 1: • Fenofibrate (414.0 kg ± 4.8 kg) and sodium laurilsulfate (14.48 kg ± 0.10 kg) are loaded into a 1750 L container with the following sequence: 46.0 kg fenofibrate + 1.810 kg sodium laurilsulfate.	Step deleted	Co-micronisation steps deleted.	The micronized grade of the API fenofibrate is being used in the new process. Therefore, this step is no more required.
	Step-2:	Step deleted	Co-micronisation steps deleted.	The micronized grade of the API fenofibrate is being used in the

	• The powder is mixed in a turn-over mixer for 30 ±10 minutes at an appropriately validated rate. Equivalent equipment with appropriately validated ranges may be used.			new process. Therefore, this step is no more required.
	Step 3: • The fenofibrate/sodium laurilsulfate co-micronisate is weighed. Lactose and pregelatinised starch are weighed, then pre-mixed for 15±5 minutes in a turn-over mixer. Fenofibrate/sodium laurilsulfate co-micronisate, lactose and pre-gelatinised starch are then loaded into the mixer-granulator. While powder is mixed by the main axis at 57 ± 5 rpm, purified water is delivered in the mixer-granulator through a pump with adjustable flow to a final target water volume of 64-66 liters using a validated water flow addition sequence. • After the wetting phase, mixing is maintained at 115 ± 10 rpm until main axis power consumption reaches 10 kw, without exceeding a 1 200 seconds duration. During the whole operation, the chopper works at 3 000 ± 150 rpm. The ranges presented for the granulation step are those validated for the Lödige® FKM 1200. Equivalent equipment with appropriately validated ranges may be used.	Step 1: Preparation of granulation solution • Add the purified water. • Add Sodium laurilsulfate and mix until completely dissolved. Step 2: Granulation **Preblending of lactose/starch:** • Load the Lactose/starch in the high shear granulator and mix. **Dry mixing of the Micronized Fenofibrate:** • Load the micronized fenofibrate in the high shear granulator and mix. **Granulation:** • Spray the granulating solution from step 1.	Sodium laurilsulfate and fenofibrate are added separately and one after the other. Blending of lactose, pregelatinized starch and fenofibrate is performed in Granulator instead of turn-over mixer. The process parameters for the granulation process are same for the approved and the proposed process, only the description has been revised	As the API has been changed from comicronized (SLS and fenofibrate) to micronized (Fenofibrate). Process has been revised as part of continuous improvement to increase the process efficiency.

	Step 4: • The granulate is transferred to the bowl of the fluid-bed dryer. The air flow is adjusted in order to prevent violent spattering of the powder toward the upper part of the apparatus. • Inlet air temperature is set at 65°C. When the outlet temperature of the air reaches 53°C and/or product temperature reaches 60°C, heating and fluidization are stopped and the powder is allowed to cool down to less than or equal to 50°C. The ranges presented for the drying step are those validated for the Glatt® WSG120. Equivalent equipment with appropriately validated ranges may be used.	Step 3: Drying • The wet granulate from step 2 is dried in a fluid bed dryer with an inlet air temperature set at approximately 65°C. The drying process is controlled with in-process tests that are summarized in Table 1.	No change	No change
	Step 5: • An adjusted amount of the external phase (crospovidone, magnesium stearate) is added to the dry powder in the fluid-bed dryer tank; the whole is unloaded through a mill. • Milling is carried out by forced passage through a screen with 0.8 mm holes. The speed of the rotor is 1 000 ± 100 rpm. The ranges are those validated for the Mill Fitzmill® D6. Equivalent equipment with appropriately validated ranges may be used. • Drying and milling are repeated for the second half of the granulate.	Step 4: Screening (Deagglomeration) • Screen the granulate from step 3 through 0.8 mm screen.	Granulate is milled excluding external phase. The external phase is sieved during weighing.	With new process modification, evaluation was done to sieve the external excipients separately using the sieve and was found to show no effect on the properties of the blend or the finished product. Therefore, it was proposed to sieve only granules in the milling step.
	Step 6: • The two parts of the batch are transferred to a 1000 L container which is charged into a turn-over mixer and mixed for 60 ± 10 minutes at an appropriately validated rate. Equivalent equipment with	Step 5: Final Blending • Manually sieve the crospovidone and magnesium stearate. Blend with the milled granules obtained in step 4.	The two parts of the batch & external phase are	Blending time has been reduced based on the process validation study

<table>
<tr><td></td><td>appropriately validated ranges may be used.</td><td></td><td>transferred to a 1000 L container and mixed for 360 rotation at 8 RPM.</td><td></td></tr>
<tr><td></td><td><u>Step 7</u>:
• The capsules are filled using an appropriate dosing disc.</td><td><u>Step 5:</u> Capsule filling
• Fill the final blend in capsules using appropriate dosing disc. The capsule filling process is controlled with in-process tests that are summarized in Table 1.</td><td>No change.</td><td>No change</td></tr>
<tr><td></td><td><u>Steps 8 and 9</u>:
• Capsules are introduced into blisters which have just been thermoformed from a polymeric film as described in Section 3.2.P.7. Blisters are then closed with a thermosealed aluminium foil. Batch number and expiry date are printed.
• Blister packs and leaflet are put into boxes on line, batch number and expiry date being printed on the box.</td><td><u>Steps 7: Blistering</u>
• The capsules are packaged into blisters. The blistering process is controlled with in-process tests that are summarized in Table 1.
<u>Steps 8: Packaging</u>
• The blister packs and leaflet are put into carton boxes online, batch no. and expiry date being printed on the box.</td><td>No change</td><td>No change</td></tr>
<tr><td>3.2.P.3.3.3</td><td><u>Step 2</u>:
Feeding flow rate of micronizer is checked every 30 minutes.
<u>Step 4</u>:
Control of the drying process requires control of the inlet and outlet air temperatures for the fluid bed dryer Glatt® WSG120 (respectively 65°C and not more than 53°C), the product temperature (not more than 60°C) and determination of the water content of the powder at the end of the drying process (not more than 3.0%, by Karl Fischer method).
<u>Step 7</u>:
At the beginning of the filling process, the filling stations are adjusted so that the mean mass of the content of 20 capsules ranges from 347 to 353 mg and the individual</td><td>Table 2: In-Process Controls for Fenofibrate 200 mg Capsules
<table>
<tr><th>Unit Operation</th><th>In-Process Control</th><th>Test or Measurement</th><th>Acceptable Range</th></tr>
<tr><td rowspan="2">Drying</td><td>Loss on drying</td><td>Halogen lamp (HR73: 4.5g /105°C / stop criterion 4 / lamp: halogen)</td><td><1.00%</td></tr>
<tr><td>Karl fisher</td><td>Average on two measures</td><td>< 3.0%</td></tr>
<tr><td rowspan="3">Capsule Filling</td><td>Visual Check</td><td>N/A</td><td>Compliant aspect</td></tr>
<tr><td>Average mass</td><td>Eur. Ph</td><td>350.0 mg ± 5%</td></tr>
<tr><td>Disintegration</td><td>Eur. Ph.</td><td>Max 15 min</td></tr>
</table></td><td>No Change. Controls have been compiled in a table.</td><td>No Change</td></tr>
</table>

mass from 333 to 367mg. During the filling process, the mean mass of content of 20 capsules is evaluated every 30 minutes.

If the mean mass of content is:

- outside the range 324 – 376 mg: filling is stopped and filling stations are adjusted as described above;
- inside the range 324 – 376 mg but outside the range 333 – 367 mg: a new determination is immediately done. If it is the same case, the filling stations are adjusted; otherwise filling is continued;
- inside the range 333 – 367 mg: production is continued.

Every hour and in case of an extended shutdown of more than 2 hours, the individual mass of filled capsules is determined and the used capsules are checked for visual defect.
Disintegration time is checked on 6 capsules at the beginning of the filling operation, after every morning start and after every change of empty capsules batch. Results are reported in the batch record and must be no more than 15 minutes.

The length of 10 capsules is checked at the beginning of the filling operation once a day and after every change of empty capsules batch. This check is also performed in case of an extended shutdown of more than 2 hours.

Step 8:
Each blister strip is printed with a batch number and expiry date.

	Individual mass	Eur. Ph.	333 to 367 mg
	Length of capsules	Limit for size 1 type capsules	19.2 ± 0.3 mm
Blistering	Blister Seal Integrity	Leak Test	All tested blisters should pass the test

	Blister sealing is checked at the beginning of the blisterisation sequence. Blister packs are plunged into an aqueous methylene blue solution during 2 minutes under 0.5 bars and checked for absence of solution intake. Step 9: The batch number and expiry date are printed on each box.			
Equipment list	• Microniser Jet Pharma® MC400, or equivalent, fed with appropriate gas • High shear mixer Lödige® FKM 1200 or equivalent. • Pump with adjustable flow. • Mill Fitzmill® D6 or equivalent, • Fluid-bed dryer Glatt® WSG120 or equivalent. • Turn-over mixer for containers. • 1 000 L and 1 750 L containers, or other container size as appropriate • Capsule filling machine GKF-Bosch® 1200 or 1500, or MG2 Futura, or equivalent.	• High shear mixer Lödige® FKM 1200 or equivalent. • Pump with adjustable flow. • Mill Fitzmill® D6 or equivalent, • Fluid-bed dryer Glatt® WSG120 or equivalent. • Turn-over mixer for containers. • 1 000 L and 1 750 L containers, or other container size as appropriate • Capsule filling machine GKF-Bosch® 1200 or 1500, or MG2 Futura, or equivalent.	Microniser Jet Pharma® MC400, or equivalent, fed with appropriate gas has been removed.	Microniser is not required after the change from comicronisate to micronised fenofibrate.

Fenofibrate Capsules 200mg – FP Mfg process change & Capsule Color Change- Minor Variation

	Test	Acceptance Criteria		Analytical Procedure	Test	Acceptance Criteria		Analytical Procedure		
		at release	during shelf-life			at release	during shelf-life			
3.2.P.5.1	**Characters**	Opaque, orange capsule size 1, containing a white or almost white powder	Opaque, orange capsule size 1, containing a white or almost white powder.	visual	**Characters**	Opaque, ochre capsule size 1, containing a whitish powder	Opaque, ochre capsule size 1, containing a whitish powder	Visual	Change in the capsule color and composition. Update of the current references. Update of the description of the powder in the capsule. References to the analytical procedures are changed.	The color of the capsules have been changed do to the removal off erythrosin, as this compound is considered that this compound in high doses could be potentially toxic. The change in the capsule color/composition has not impact of the drug product quality. The description of the dosage form is harmonized. The references to the analytical methods are changed to the new naming of the documented system used in Abbott.
	Identification				**Identification**					
	Identification of fenofibrate by HPLC	Retention time of main peak identical with that of the reference	-	SOLID 1000122058	Identification of fenofibrate by HPLC	Retention time of main peak identical with that of the reference	-	RDAPDP003003		
	Identification of fenofibrate by TLC[1]	Rf of the main spot identical with that of the reference	-	SOLID 1000122058	Identification of fenofibrate by TLC[1]	Rf of the main spot identical with that of the reference	-	RDAPDP003002		
	Tests				**Tests**					
	Content average mass	332.5 to 367.5 mg	332.5 to 367.5 mg	Ph. Eur. 2.9.5[3]	Content average mass (mg)	332.5 to 367.5 mg	332.5 to 367.5 mg	Ph.Eur.2.9.5[3]		
	Mass uniformity	Complies with the requirements of the Eur. Ph. (±7.5%)	-	Ph. Eur. 2.9.5[3]	Mass uniformity	Complies with the requirements of the Eur. Ph. (±7.5%)	-	Ph. Eur. 2.9.5[3]		
	Disintegration time	≤ 15 minutes	≤ 15 minutes	SOLID 1000122058	Disintegration time	≤ 15 minutes	≤ 15 minutes	Ph. Eur. 2.9.1[3]		
	Dissolution test (average of 6 capsules)	20 minutes: ≥ 75% 40 minutes: ≥ 90%	20 minutes: ≥ 70% 40 minutes: ≥ 85%	SOLID 1000122058	Dissolution test	Q_{20} = 75% Q_{40} = 90%	Q_{20} = 70% Q_{40} = 85%	RDAPDP002747		
					Degradation products/Impurities (HPLC):[1] Impurity A	≤ 0.1%	≤ 0.1%	RDAPDP003004		

	Degradation products:[1] Impurity A Impurity B Unspecified impurities Total of impurities	≤ 0.1%[4] ≤ 0.1%[4] ≤ 0.1% each[4] ≤ 0.3%[4]	≤ 0.1%[4] ≤ 0.1%[4] ≤ 0.1% each[4] ≤ 0.3%[4]	SOLID 100012205 8	Impurity B Unknown impurities Total of impurities	≤ 0.1% ≤ 0.1% each ≤ 0.3%	≤ 0.1% ≤ 0.1% each ≤ 0.3%			
	Microbiological contamination [2]	Ph. Eur.5.1.4[3] (nonaqueous preparations for oral use)	Ph. Eur.5.1.4[3] (nonaqueous preparations for oral use)		Microbiological contamination[1, 0]	Ph. Eur.5.1.4[3] (nonaqueous preparations for oral use)	Ph. Eur.5.1.4[3] (nonaqueous preparations for oral use)			
	TAMC (total aerobic microbial count)	NMT 10^3 CFU/g	NMT 10^3 CFU/g	Ph. Eur. 2.6.12[3]	TAMC (total aerobic microbial count)	NMT 10^3 CFU/g	NMT 10^3 CFU/g	Ph. Eur. 2.6.12[3]		
	TYMC (total combined yeast/moulds count)	NMT 10^2 CFU/g	NMT 10^2 CFU/g	Ph. Eur. 2.6.12[3]	TYMC (total combined yeast/moulds count)	NMT 10^2 CFU/g	NMT 10^2 CFU/g	Ph. Eur. 2.6.12[3]		
	Escherichia coli	Absent/g	Absent/g	Ph. Eur. 2.6.13[3]	Escherichia coli	Absent/g	Absent/g	Ph. Eur. 2.6.13[3]		
	Assay				**Assay**					
	Assay of fenofibrate	190.0 to 210.0 mg	190.0 to 210.0 mg	SOLID 100012205 8	Assay of fenofibrate	190.0 to 210.0 mg/capsule (95.0 to 105.0% LC)	190.0 to 210.0 mg/capsule (95.0 to 105.0% LC)	RDAPDP0 03003		
	[1] No routine test [2] To be performed on every 10th batch [3] Current edition [4] Percentage of the fenofibrate label claim				[1] No routine test [2] Every 10 batches [3] Current edition					
3.2.P.5.2	**Dissolution for Stability (Ph. Eur. 2.9.3, current. ed).** The dissolution test is performed using: • a paddle apparatus;				**Dissolution for Stability (Ph. Eur. 2.9.3, curr. ed.)** This method should only be used once the dissolution results are not complying to the specifications with method 1.1 described above. This means cross-linking of the capsules				Alterations to the dissolution method used in stability	The method use is changed in order to be aligned with the EP guidelines on crosslinking and

	• a rotation speed 90 rpm ± 4%; • Dissolution medium: In the vessel, add 500 ml of aqueous solution of pancreatin at 35 mg/l in phosphate buffer pH=8, 1 capsule and allow the pancreatin to operate during 30 minutes, then add 500 ml of 0.2 M aqueous solution of sodium laurylsulfate. Pancreatin is added to produce not more than 1750 USP Units of protease activity per 1000 ml of the dissolution test medium. Other pancreatin concentrations may be used depending on the protease activity per mg. The sodium laurylsulfate having an inhibitory effect on the pancreatin, the hydrolysis of the gelatin is carried out before the addition of the aqueous sodium laurylsulfate solution. In order to have a final concentration of 0.1 M in sodium laurylsulfate in the dissolution medium, a 0.2 M aqueous sodium laurylsulfate solution is used to make up to the volume. • A reference solution is prepared as follows: To prepare in duplicate, dissolve 20.0 mg of fenofibrate with 10.0 ml of acetonitrile, and dissolve on a magnetic stirrer for 15 minutes. Complete to 200.0 ml with dissolution medium (being 50:50 V/V of pancreatin at 35 mg/l in phosphate buffer pH=8 and 0.2 M aqueous solution of sodium laurylsulfate). Dilute this solution to 10 times its volume with dissolution medium (being 50:50 V/V of pancreatin at 35 mg/l in phosphate buffer pH=8 and 0.2 M aqueous solution of sodium laurylsulfate).	have occurred and pancreatin must be used to break the cross-linking bonds. The dissolution test is performed using: • a paddle apparatus; • a rotation speed 90 rpm ± 4%; • Preparation of reagents; Phosphate buffer pH 8.0 (Solution A) - 1250 ml KH_2PO_4 0.20 M (e.g. weigh 54.5 g of KH_2PO_4 in a graduated flask of 2 liters, make up to volume with water). - 1152.2 mL of NaOH 0.20 M (e.g. weigh 16.0 g of NaOH flakes in a graduated flask of 2 liters, make up to volume with water). - Mix the two solutions and make to volume (5 liters) with water. Pancreatin solution (Solution B) Prepare 5 liters solution with 35 mg/L of pancreatin in solution A. Pancreatin is added to produce not more than 1750 USP Units of protease activity per 1000 ml of dissolution medium. Other pancreatin concentrations maybe used depending on the protease activity per mg. Dissolution Medium part 1 500 ml of solution B. Degas and heat to 37 °C ± 0.5°C. Dissolution Medium part 2	made. The method should only be used once crosslinking in the capsules are seen and not at each time point of the stability. The addition of the capsule in first media (pancreatin) is the actual start of the dissolution in the updated method, after 10 minutes the SLS media is added. No change the composition to the media.	testing with enzymes. The set-up of the dissolution (start of actual dissolution) is aligned with EP guidelines on testing cross linked capsules.

	• A UV-visible spectrophotometer set to 290 nm and fitted with cells of 10 mm path length. Introduce in each of the six vessels a capsule previously weighed with a stainless steel piece. The capsules must be at the bottom of the vessel. At times 20 and 40 minutes: • Take a sample of 5 ml in each vessel through a filter (porosity 10 to 20 µm); • Add immediately 5 ml of new medium in each of the 6 vessels. • Dilution: in a 25 ml volumetric flask, introduce 1 ml of each sample and complete to 25.0 ml with sodium laurylsulfate solution. Determine the absorbance of the solution at λ max. near 290 nm. Use the dissolution medium as blank. The ratio of absorbance of the 2 reference solutions must range between 98.0% and 102.0%. The percentage of fenofibrate dissolved when pancreatine is used must be ≥ 70% at 20 minutes and ≥ 85% at 40 minutes.	0.2 M Sodium lauryl sulfate solution: weigh 57.68 g of Sodium lauryl sulfate per liter of water and dissolve. Degas and heat to 37 °C ± 0.5°C. Diluent Mix 500 ml of dissolution medium part 1 with 500 ml of dissolution medium part 2; • A reference solution is prepared as follows: (prepare in duplicate) · Accurately weigh 20.0 mg of Fenofibrate ARS into a 200-ml volumetric flask and dissolve with 10.0 ml of acetonitrile. · Magnetically stir for 15 minutes. Complete to 200.0 mL with diluent. · Dilute this solution to 10 times its volume with diluent. For Online sampling: (prepare in duplicate) · Accurately weigh 20.0 mg of Fenofibrate ARS into a 100-ml volumetric flask and dissolve with 5.0 ml of acetonitrile. · Magnetically stir for 15 minutes. Complete to 100.0 mL with diluent. Standard solutions are stable for 4 days at 15-30°C stored in clear glassware. • A UV-visible spectrophotometer set to 290 nm and fitted with cells of 10 mm path length. • Procedure for Dissolution;		

		• Transfer 500 mL of dissolution medium part I to the 6 dissolution vessels. • Allow the media to reach 37.0 ± 0.5°C. • Introduce in each of the six vessels a capsule previously weighed with a stainless-steel sinker. • The capsules must be at the bottom of the vessel and start stirring. • After 10 minutes add 500 ml of pre-heated dissolution medium part 2 to the 6 dissolution vessels. • After 20 minutes and 40 minutes after introduction of the capsules, withdraw an aliquot of about 5 mL from each vessel and immediately add 5 mL of new dissolution medium. * **If subsequent samples are taken from the dissolution vessels, correct for the decreased volume and withdrawn Fenofibrate.* • Filter each of the specimens through suitable sample preparation filters, discarding the first 2 mL. • Allow the sample specimens to cool down to ambient temperature. For off-line sampling: • Pipette 1.0 ml of the sample into a 20-ml volumetric flask and complete to 20.0 mL with dissolution medium (for capsule of 200 mg) • Measure each of sample specimens at 290 nm, using dissolution medium as a blank. Sample solutions are stable for 4 days at 15-30°C stored in clear glassware.		

		• Determine the absorbance of the solution at λ max. near 290 nm. Use the dissolution medium as blank. The ratio of absorbance of the 2 reference solutions must range between 98.0% and 102.0%. • Evaluate the results, using the acceptance criteria in the current specification document and Ph.Eur. 2.9.3 (Dissolution). If required, analyze more capsules.		
3.2.P.5.3	**Dissolution for Stability:** **Additional Validation for the Use of Pancreatin** Additional validation tests have been performed with pancreatin on capsules containing 267 mg of micronised fenofibrate. The Fenofibrate Capsule 267 mg represents all strengths since the only relevant difference is the quantity of product filled into the capsules. **1.1.1 Specificity** Specificity has been tested regarding the dissolution medium, a solution of pancreatin in phosphate buffer pH=8, excipients, and absorbance due to the empty capsule. For all the solutions tested, the maximum interference found was the interference due to the solution of pancreatin, corresponding to 0.4% of fenofibrate dissolved : this quantity may be considered negligible. The method is thus specific for the assay of fenofibrate after dissolution of 267 mg micronised fenofibrate capsules in 0.1 M aqueous solution of (pancreatin/sodium laurylsulfate).	**Dissolution for stability:** **Summary** This report describe the validation parameters which have been performed to validate the procedure used to determine the dissolution by UV-spectrometry of Fenofibrate in cross linked capsules of 67 mg, 200 mg and 267 mg. The method, described in DARIUS RDAPDP002747 is validated for the listed in Table 6 as described in ICH Guideline Q2(R1). The validation confirms the acceptability of the analytical procedure with respect to the all excipients. **Table 7. Validation Parameters for DARIUS RDAPDP002747, Fenofibrate capsules, 67 mg, 200 mg and 267 mg** **Parameter** | **Criteria** | **Result**	The updated method for stability with enzymes has been validated in accordance with ICH requirements.	The updated method requires validation in accordance with ICH requirements.

1.1.2 Outset for the Dissolution Test

During the enzymatic hydrolysis step (30 minutes), the amount of fenofibrate dissolved in the solution of pancreatin in phosphate buffer pH=8 is 1 mg. This amount corresponding to 0.4% is negligible.

According to this result :

- the outset for the dissolution test with pancreatin is the addition of the 0.2 M aqueous solution of sodium laurylsulfate,
- the determination of the amount of fenofibrate dissolved at the end of the enzymatic hydrolysis step will not be performed in routine test.

1.1.3 Linearity

The linearity study is performed on 3 separate days by the same operator working on the same equipment.

- Linearity of fenofibrate in the reference solutions: Each day, 7 independent reference solutions containing 2, 3, 6, 8, 10, 12 and 15 µg/ml of fenofibrate, respectively corresponding to 15% to 112.5% of the theoretical concentration (10 µg/ml), are prepared and analysed by UV spectrophotometry.The absorbances obtained against 0.1 M aqueous solution of (pancreatin/sodium laurylsulfate) are collected. Cells with a 10 mm pathlength were used to determine the linear range of the method. The data obtained are presented in Table 3 hereafter.

Specificity	No interference to be detected at the wavelength of the compound of interest, the absorbance should be ≤2%	No interference was detected at the wavelength used of Fenofibrate.
Linearity	Correlation Coefficient is greater than 0.99 for Fenofibrate Intercept must be either not significant of analytically not relevant |Y-intercept/b-slope| ≤ 3.0%	Fenofibrate: 7 levels 10% – 160%, r = 0.999901. The intercept is significant but analytically not relevant
Accuracy	The mean recovery and 90% confidence interval of the main component is within 95.0 - 105.0% of the theoretical concentration. The individual recovery of the main component is within 90.0 - 110.0% of the theoretical concentration. The intercept and slope of the	Fenofibrate: 7 levels 10% – 160%, six replicates. Mean recovery = 100.0%, CI = 99.4% - 100.6% The individual recoveries are within 90.0 – 110.0% of the theoretical concentration.

Table 3. Linearity results of Fenofibrate in the Reference Solutions

Group	Series	Quantity (µg/ml)	Signal (AU)
15	1	2.079	0.0911
15	2	2.138	0.0981
15	3	1.981	0.0824
22.5	1	3.014	0.1362
22.5	2	3.095	0.1448
22.5	3	3.050	0.1272
45	1	6.120	0.2924
45	2	6.018	0.2755
45	3	5.886	0.2594
60	1	8.168	0.3624
60	2	8.232	0.3761
60	3	8.324	0.3188
75	1	10.095	0.4531
75	2	10.090	0.4645
75	3	9.89	0.4227
90	1	12.585	0.5859
90	2	12.100	0.5574
90	3	10.730	0.4551
112.5	1	14.670	0.6794
112.5	2	15.195	0.7023
112.5	3	15.670	0.6766

Theoretical amount at the 75% level : 10 µg/ml

	accuracy compared to linearity should be either: 1) statistically not significant, signifying compatibility of intercept and slope with 0 and 1, respectively, at the 99% confidence interval 2) analytically not relevant, signifying that the mean and 90% confidence interval of the recovery based on accuracy compared to linearity for Fenofibrate must lay between 95.0% and 105.0%	The intercept is not significantly different from 0, and the slope is 1.00318
Range	The test method is linear, precise, and accurate covering the range of at least 10 - 130%.	The test method is linear, precise, and accurate covering the range of 10 - 159% nominal concentration of Fenofibrate. (0.02 – 0.32 g/ml)

The unweighted linear least squares regression analysis is performed on the 21 couples of data obtained. The X-Y plot is presented in Figure 1 hereafter:

(Y = signal (AU) ; X = quantity of fenofibrate (µg/ml))

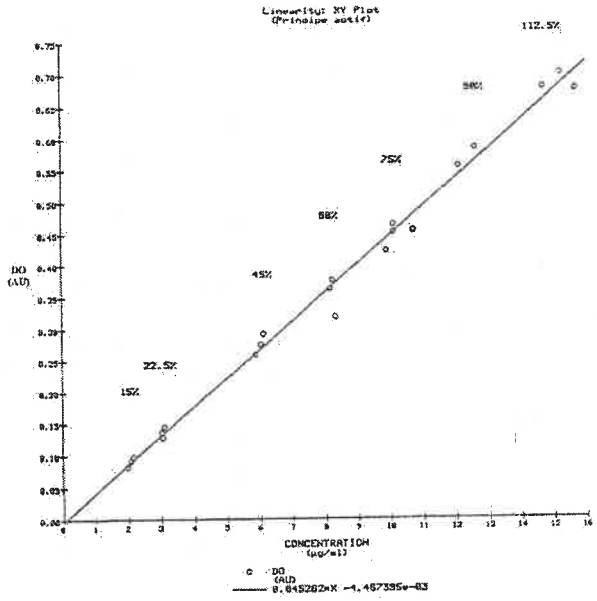


Figure 1. Linearity of Fenofibrate in the Reference Solutions

The statistical tests carried out indicate:

- homogeneity of variances between the levels tested

Precision	Repeatability; Six determinations, 2 days, two analysts - CV% must be ≤ 3.0% Intermediate precision; ; Six determinations, 2 days, two analysts - CV% must be ≤ 4.0%	Individual and mean results were within specification - Repeatability CV% = 0.7% - Intermediate precision CV% = 2.6%
Detection Limit	For information	LOD = 1.7% (= 0.0034 mg/ml)
Quantitation Limit	LOD ≤ 10%	LOQ = 7.3% (= 0.015 mg/ml)

- existence of a relationship between signal (AU) and amounts
- linearity of this relationship
- Y-intercept not different from 0 at the significance level of 5%.

Linearity of fenofibrate in the reference solutions is thus demonstrated, with :

- equation of the regression line : $Y = 0.045262\,X + 0.00447$
- correlation coefficient (r) = *0.996*

- Linearity of fenofibrate in the test solutions (obtained from the reconstituted dosage form):

Each day, 3 independent test solutions are prepared by spiking a placebo placed in the conditions of the dissolution test method, with a quantity of fenofibrate corresponding to 7.4, 10 and 12.7 µg/ml of fenofibrate concentration in the test solutions.

The data obtained are presented in Table 4 hereafter.

Table 4. Linearity Results of Fenofibrate in the Reconstituted Dosage Form

Group	Series	Quantity (µg/ml)	Signal (AU)
55	1	7.336	0.3396
55	2	7.401	0.3297
55	3	7.350	0.3363
75	1	10.090	0.4671
75	2	10.022	0.4576

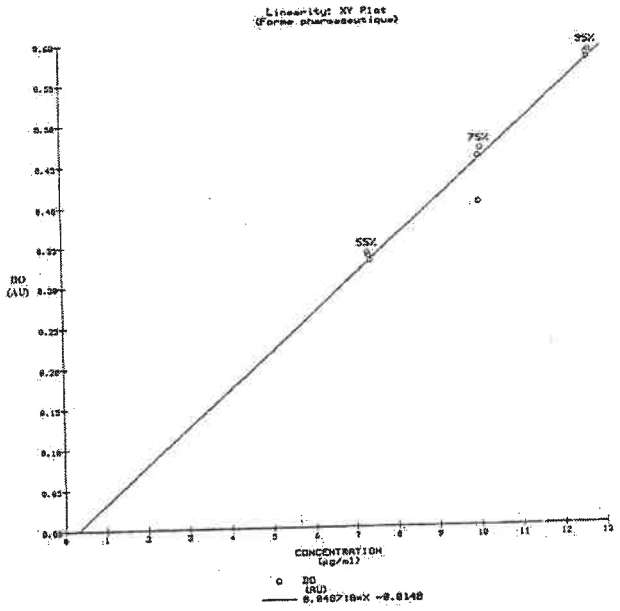
Robustness of the method	The mean ratio of automated versus manual sampling and 90% confidence interval must be between 90.0 - 110.0% for the 20 minutes time point. The mean ratio of automated versus manual sampling and 90% confidence interval must be between 96.0 - 104.0% for the 40 minutes time point.	- 20 minutes: The mean and 90% confidence interval for Fenofibrate is 102.8 – 106.0% (mean = 104.4%) - 40 minutes: = The mean and 90% confidence interval for Fenofibrate is 98.9 – 100.3% (mean = 99.6%)
Robustness of the UV-method	The normalized mean A(1% 1cm) and 90% confidence interval must be between 98.0 - 102.0%.	The mean and 90% confidence interval for Fenofibrate is 98.9 – 99.7%
Stability of Solution	The mean and 90% confidence interval must be between 95.0 - 105.0%	The mean and 90% confidence interval for Fenofibrate is 100.5% - 103.4% (mean = 101.9%)

The validation data for each parameter is described in detail in 3.2.P.5.3 in the individual sections. Based on the validation data presented, this method is valid for its intended use for the dissolution of Fenofibrate in

75	3	10.032	0.4028
95	1	12.666	0.5786
95	2	12.655	0.5847
95	3	12.713	0.5874

The unweighted linear least squares regression analysis is performed on the 9 couples of data obtained. The X-Y plot is presented in Figure 2 hereafter:

Y = signal (AU); X = fenofibrate concentration (µg/ml).



Fenofibrate capsules containing 67 mg, 200 mg and 267 mg of Fenofibrate.

Figure 2. Linearity of Fenofibrate in the Reconstituted Dosage Form

The statistical tests carried out indicate:

- homogeneity of variances between the levels tested
- existence of a relationship between signal (AU) and amounts
- linearity of this relationship
- Y-intercept not statistically different from 0 at the significance level of 5%

Linearity of fenofibrate in the reconstituted dosage form is thus demonstrated, with :

- equation of the regression line : $Y = 0.046718\,X - 0.0148$
- correlation coefficient (r) = *0.984*

- Comparison between linearity of fenofibrate in reference solutions and in reconstituted dosage form:

The linear curve parameters obtained with the reference solution are compared to those of the linear curve obtained in the reconstituted dosage form, in order to demonstrate that the 2 curves are not significantly different. This comparison is presented in Figure 3 hereafter.

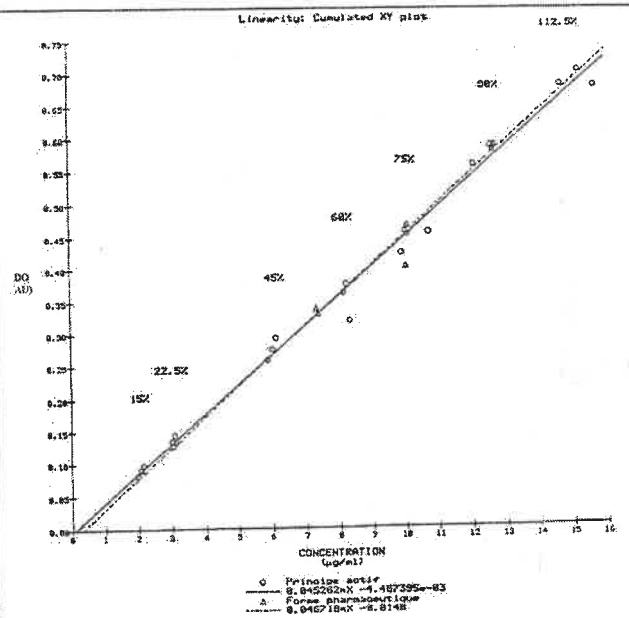


Figure 3. **Linearity of Fenofibrate in the Reference Solutions and in the Reconstituted Dosage Form**

The statistical analysis shows that the slopes and intercepts of reference solution and of reconstituted dosage form are not significantly different, at 5% significance level, indicating the absence of matrix effect.

Conclusion

The method is linear within 7.4 µg/ml and 12.7 µg/ml of fenofibrate dissolved in 0.1 M aqueous solution of

pancreatin/sodium laurylsulfate, for 10 mm pathlength cells.

1.1.4 Accuracy

Accuracy is determined from the fenofibrate linearity data in the test solutions, i.e. at 7.4, 10.0 and 12.7 µg/ml concentrations.

Recovered amounts are calculated from the spectrophotometric data, using a 100% reference solution.

Recovery values are then calculated between recovered amounts and actual concentrations of fenofibrate dissolved (level 75%),as described in the linearity study. The data are presented in table 6 hereafter.

Statistical tests indicate:

- homogeneity of variances between the levels tested
- absence of significant differences regarding within and between-groups variations

The mean recovery is *101.5%* and the 95% confidence interval is *[98.0% ; 105.0%]*, which is satisfactory.

Table 5. Accuracy Data

Group	Series	Quantity (µg/ml)	Recovered qty (µg/ml)	Recoveries (%)	Variances
55	1	7.336	7.566	103.14	
55	2	7.401	7.162	96.77	26.94

55	3	7.350	7.869	107.05	
75	1	10.090	10.407	103.14	21.28
75	2	10.022	9.940	99.18	
75	3	10.032	9.424	93.14	
95	1	12.666	12.891	101.78	17.02
95	2	12.655	12.701	100.36	
95	3	12.713	13.744	108.11	

Conclusion

The method is accurate within the range 7.4 µg/ml to 12.7 µg/ml of fenofibrate dissolved in 0.1 M aqueous solution of pancreatin/sodium laurylsulfate.

1.1.5 Precision

Precision was performed on 3 separate days by 2 different operators working on the same equipment.

Each day, calibration was performed as indicated in the dissolution test method.

Each day, 1 dissolution test is performed from 6 capsules, corresponding to a theoretical final concentration of 10.68 µg of fenofibrate /ml of dissolution medium.

The quantities of fenofibrate dissolved (%) are presented in Table 6 thereafter.

Table 6. Precision Data

Series	Test	Fenofibrate dissolved at	
		20 minutes	40 minutes
1	1	84.57	89.04
1	2	84.95	88.21
1	3	84.36	88.41
1	4	85.40	88.25
1	5	83.68	87.94
1	6	84.74	88.21
2	1	89.69	94.17
2	2	89.67	93.54
2	3	89.25	93.33
2	4	89.68	93.56
2	5	89.48	92.55
2	6	89.78	92.85
3	1	88.69	93.92
3	2	90.68	96.90
3	3	92.79	94.70
3	4	90.31	96.14
3	5	90.89	95.47
3	6	89.61	94.99

Preliminary statistical test indicate a good homogeneity between the series tested.

Then the calculations give:

	• a relative standard deviation for repeatability (RSD_r) = 1.0% at 20 minutes and 0.8% at 40 minutes; • a relative standard deviation for intermediate precision (RSD_R) = 3.7% at 20 minutes and 4.0% at 40 minutes. **1.1.6 Range** Regarding the data obtained above, the interval of the method may be defined within 7.4 µg/ml and 12.7 µg/ml of fenofibrate dissolved in 0.1 M aqueous solution of (pancreatin/sodium laurylsulfate), for 10 mm pathlength cells, i.e. approximately from 70% to 120% of the theoretical amount (267 mg per capsule, or 10.68 µg/ml in the test solution).			
3.2.P.5.3	**Validation TLC for ID** No validation data available	**Validation TLC-method for ID** **Introduction and Summary** The TLC method used for the identity of Fenofibrate capsules containing 200 mg Fenofibrate has been validated for specificity. Identification of Fenofibrate by TLC using silica gel coated glass plate with fluorescence indicator and UV detection at 254 nm. **Specificity** In order to verify the specificity of the analytical procedure the following readings were performed with UV (1cm cuvette): - Diluent - Fenofibrate standard solution - Placebo mixture solution - Solution of reconstituted pharmaceutical form - Test solution (3 batches of 200 mg capsules)	Performed method validation for TLC method for ID.	Method validation was not performed.

The results are summarized in Table 8.

Table 8 Results Specificity

	Spot at the same Rf of Fenofibrate	Colour intensity spot same as Fenofibrate (80 to 120% of the theoretic colour intensity)
Diluent	No	n.a.
Fenofibrate standard	Yes	Complies
Placebo mixture	No	n.a
Reconstituted pharmaceutical form	Yes	Complies
Test solutions		
200 mg, batch 24925	Yes	Complies
200 mg, batch 25984	Yes	Complies
200 mg, batch 26554	Yes	Complies

Summary:

1. Unit formula composition:
There is no change in the unit formula composition of the drug product for the approved and proposed process. Therefore, no affect on the critical quality attributes of the drug product is anticipated.

2. Batch Formula:
There is no major change in the manufacturing formula. Only the number of capsules has been changed from 982,200 to 982,114. The batch formula for the production of final blend remains unchanged. Therefore, there is no impact on the product quality.

3. Manufacturing Process, equipment and process controls:
There is a minor change in the manufacturing process steps as the comicronisation step has been removed. Micronised Fenofibrate is used in the proposed manufacturing process. All other critical process parameters are either same or have been evaluated during the manufacturing of the validation batches. The evaluated process parameters for the proposed process is efficient and reproducible to produce the same quality of product as for the approved process. The equipment involved in the production of the batches at both the scales have similar operating principles. The process is controlled through the in-process control tests at different stages that are same for both the processes.

4. Analytical methods
The TLC method which was already in place was never validated. The method validation data of the TLC-method is now included.

5. Comparison of the physicochemical properties of the drug product:
It is evident from the comparison that all the critical quality attributes of the drug product are similar for both the processes. Thus, it can be concluded that there is no impact of process change on the quality of the drug product pre-change and post-change.

6. Stability of the drug product:
According to the stability data 3.2.P.8, it is clear that the drug products manufactured using the comicronised or the micronised process are very stable for upto 6 months when stored at the recommended storage condition. There is no significant difference between the product characteristics of both the processes during the release and shelf life.

Conclusion:

Based on the above comparison tables and summary, it can be concluded that there is no impact of the process change on the drug product quality attributes and both the products (pre-change and post-change) are essentially similar.

3.2.S.4.1 Specification

Test	Registered Specifications	Test	Proposed Specifications	Summary of the change	Reason for the change
Characteristics	Crystalline, white or almost white powder, **practically insoluble in water, very soluble in methylene chloride and slightly soluble in ethanol.**	Appearance	White or almost white, crystalline powder	Solubility test removed from description and include as each individual tests	Editorial change
		Solubility			
		Water	Practically insoluble		
		Ethanol	Slightly soluble		
		Methylene Chloride	Very soluble		
Identification		Identification			
Melting point	79 to 82°C	Melting point, in °C	79 - 82	No changes	Not applicable
Infrared spectrum	Identical with CRS reference spectrum	IR spectrum	Corresponds to spectrum of the reference standard	No changes	Not applicable
Appearance of solution	The solution is clear and not more intensely colored than reference solution BY6	Appearance of solution	The solution is clear and not more intensely colored than reference solution BY_6	No changes	Not applicable
Acidity	≤ 0.2 ml NaOH 0.1 M	Acidity, in ml NaOH 0.1 M	≤ 0.2	No changes	Not applicable
Related substances		Related substances			
Impurity A	≤ 0.1%	Impurity A (HPLC, % w/w)	**≤ 0.15**	Relaxed impurity limits	As per EP monograph
Impurity B	≤ 0.1%	Impurity B(HPLC, % w/w)	**≤ 0.15**		
Impurity C, D, E, F	≤ 0.1% each			Removed impurities test for C, D, E, F	
Impurity G	≤ 0.2%	Impurity G (HPLC, % w/w)	≤ 0.2	No changes	Not applicable
Unidentified impurities	≤ 0.10% each	unspecified impurities content (HPLC, % w/w)	≤ 0.10	No changes	Not applicable
Total of impurities	≤ 0.5%	Sum of Impurities (HPLC, % w/w)	≤ 0.5	No changes	Not applicable
Halides	≤ 100 ppm (expressed as chlorides)	Halides (expressed as chlorides), in ppm	≤ 100	No changes	Not applicable
Sulphates	≤ 100 ppm	Sulphates, in ppm	≤ 100	No changes	Not applicable

Heavy metals	**≤ 20 ppm**			Heavy metal test removed	As per ICH Q3D requirements.
Loss on drying	≤ 0.5%	Loss on drying, in % m/m	≤ 0.5	No changes	Not applicable
Sulphated ash	≤ 0.1%	Sulphated ash, in % m/m	≤ 0.1	No changes	Not applicable
Particle size		Particle size, in µm			
Particles of Ø < 630 µm	≥ 99.0%	**D50**	**≤15 µm**	Update of PDS limits	Due to the change in the finished product manufacturing process the PSD limits are updated.
Particles of Ø < 400 µm	≥ 90.0%	**D90**	**≤25 µm**		
		D99	**≤50 µm**		
Assay (on dry product)	98.0 to 102.0%	Assay (on dry substance) according to EP (%w/w)	98.0 – 102.0	No changes	Not applicable