Regulatory Compliance in Artwork:

Regulatory Impact Assessment for Technical changes in Artwork

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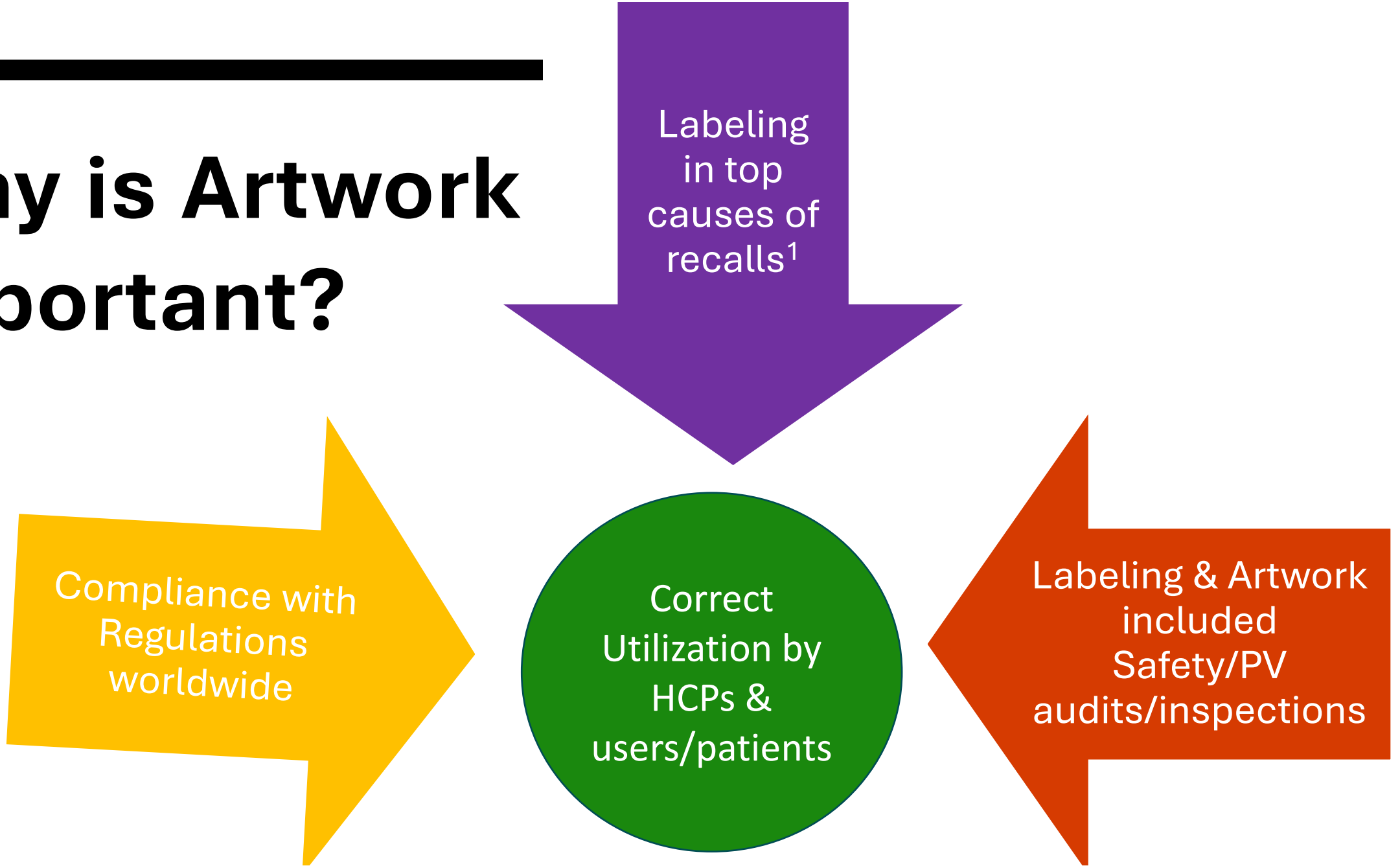
Why is Artwork important?



[1]Kelsey Hall, Tyler Stewart, Jongwha Chang, Maisha Kelly Freeman, Characteristics of FDA drug recalls: A 30-month analysis, *American Journal of Health-System Pharmacy*, Volume 73, Issue 4, 15 February 2016, Pages 235–240, https://doi.org/10.2146/ajhp150277

Why is Artwork important?

Other reasons:

- Let’s discuss in the next round table Discussion

Labeling & Artwork concepts in Regulatory

Content (Labeling)

- ✓ Reflects Company and HA-approved **information on the use of the product, safety & efficacy.**
- ✓ *Word or PDFs** files containing TEXT in local templates for submission/notification to HA. Associated to HA Marketing Authorizations.

Types of Local Labeling:

a. **Physician/HCP information** (USPI, Prescribing Information, Physician Circular, SmPC, etc)

b. **Patient/User Information** (Patient Leaflet, User Leaflet, Medication Guide, etc.)

c. **Instructions For Use**

d. **Packaging text** (QRD-like, or other local templates containing the text for primary and secondary packaging such as foil, labels, cartons, etc.)

Technical & Design (Artwork)

- ✓ **Graphical representation of Regulatory content added to a specified format and structure with given dimensions and shaped into a layout according to the company trade dress and style.**

Artwork components are associated to SKUs & Markets. Artwork Regulatory content is based on the local labeling:

- ✓ Leaflet
- ✓ Carton
- ✓ Foil/Blister
- ✓ Vial/Syringe Label
- ✓ Etc.

*new formats: xml, html, etv

Let us align on this project – we have done a lot already!

Country	Mandatory/ Voluntary	Law – link on E-PI	OGN implement-tation	Removal of Paper Insert	Effective Date	Remarks
Japan	Mandatory	Use PMDA website stacked code	Use PMDA website stacked code	√	1 Aug 2023	XML, Linking to E-PI text in HA portal
Australia	Mandatory	Mandatory Human readable reference to HA site + voluntary QR Code	Human readable reference to HA site	√	Before 2020	PDF, except Oral Contraceptive
Thailand	Mandatory	QR Code	QR code	√	23 June 2023	PDF
Singapore	Voluntary	QR Code	QR Code	X	2019	Html, Webpage
Malaysia	Voluntary	QR Code	QR Code	X	1 May 2023	PDF
Indonesia	Voluntary	2D Matrix + HA app	2D Matrix + HA app	X	1 Oct 2023	PDF
Taiwan	Voluntary	QR Code	QR Code	X	July 2022	PDF, Hospital use injectables only. OOS for OGN now.
China	Voluntary	QR Code	-	X	29 June 2023	Html, Webpage

Country	Mandatory/ Voluntary	Law – link on E-PI	OGN implement -tation	Removal of Paper Insert	Effective Date	Remarks
Jordan	Mandatory	2D Matrix Barcode/QR Code	-	x	18 Jan 2025	XML, JFDA implements FHIR standards
Turkey	Mandatory	QR Code	-	x	1 Jan 2026	Audible & Readable PI link to HA website
European Union	Mandatory	2D Data Matrix /QR Code	-	x	1 Jan 2027 (tentative)	XML, EMA implements FHIR standards
Italy	Voluntary	2D Data Matrix /QR Code	-	X	April 2016	national pilot, Html/webpage Note: part of broader EU ePI initiatives
Belgium-Luxembourg	Voluntary	2D Data Matrix /QR Code	-	X	Aug 2018	national pilot extend until Aug 2025 Note: part of broader EU ePI initiatives
Germany	Voluntary	2D Data Matrix /QR Code	-	X	Since 2009	national pilot, XML,the app is available at: https://gebrauchsinformation4-0.de Note: part of broader EU ePI initiatives
Brazil	Voluntary	QR Code	-	x	May 2022	Online access ie PDF, Html/Webpage
Argentina	Voluntary	2D Data Matrix /QR Code	-	x	2025	Mandatory by 2026

Package leaflet: Information for the user

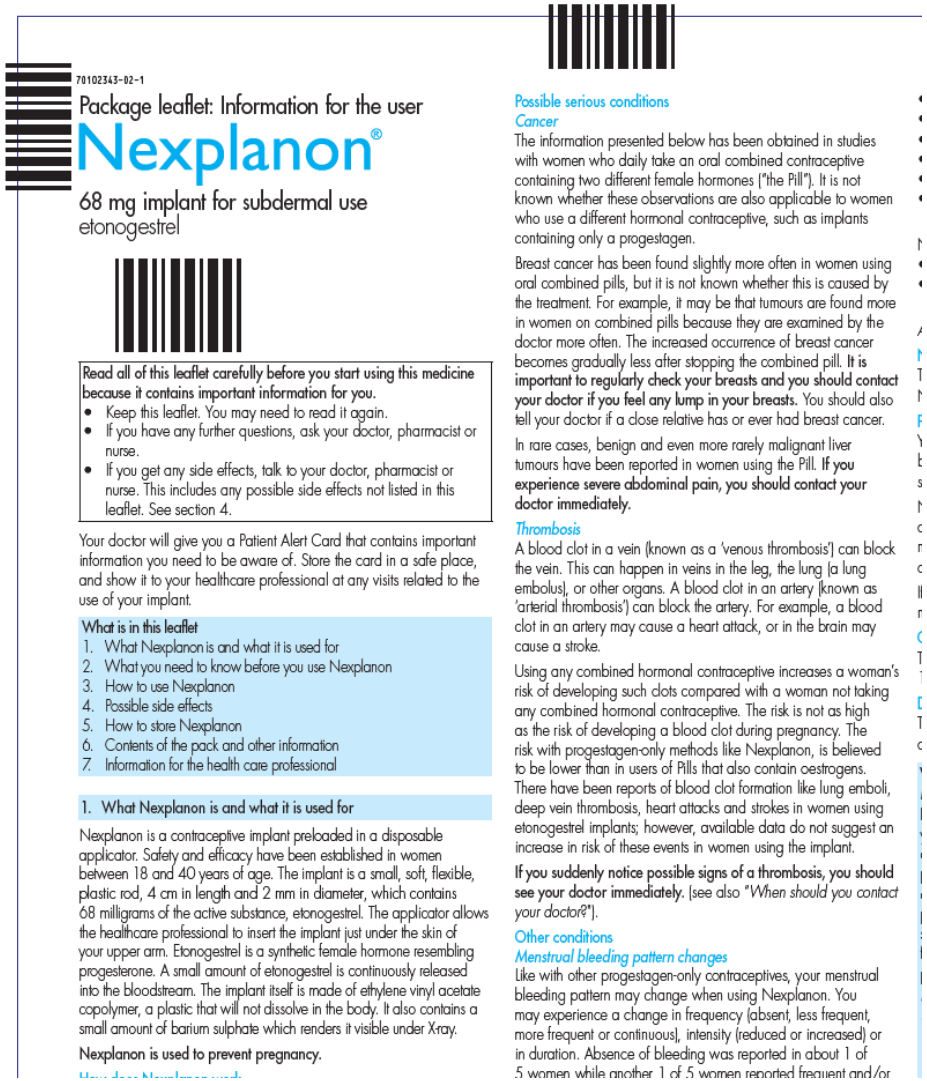
Nexplanon® 68 mg implant for subdermal use
etonogestrel

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

Your doctor will give you a Patient Alert Card that contains important information you need to be aware of. Store the card in a safe place, and show it to your healthcare professional at any visits related to the use of your implant.

What is in this leaflet

Labeling User/Patient information (content)



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What is in this leaflet

1. What Nexplanon is and what it is used for

Nexplanon is a contraceptive implant preloaded in a disposable applicator. Safety and efficacy have been established in women between 18 and 40 years of age. The implant is a small, soft, flexible, plastic rod, 4 cm in length and 2 mm in diameter, which contains 68 milligrams of the active substance, etonogestrel. The applicator allows the healthcare professional to insert the implant just under the skin of your upper arm. Etonogestrel is a synthetic female hormone resembling progesterone. A small amount of etonogestrel is continuously released into the bloodstream. The implant itself is made of ethylene vinyl acetate copolymer, a plastic that will not dissolve in the body. It also contains a small amount of barium sulphate which renders it visible under X-ray.

Nexplanon is used to prevent pregnancy.

Possible serious conditions

Cancer

The information presented below has been obtained in studies with women who daily take an oral combined contraceptive containing two different female hormones ("the Pill"). It is not known whether these observations are also applicable to women who use a different hormonal contraceptive, such as implants containing only a progestagen.

Breast cancer has been found slightly more often in women using oral combined pills, but it is not known whether this is caused by the treatment. For example, it may be that tumours are found more in women on combined pills because they are examined by the doctor more often. The increased occurrence of breast cancer becomes gradually less after stopping the combined pill. **It is important to regularly check your breasts and you should contact your doctor if you feel any lump in your breasts.** You should also tell your doctor if a close relative has or ever had breast cancer.

In rare cases, benign and even more rarely malignant liver tumours have been reported in women using the Pill. **If you experience severe abdominal pain, you should contact your doctor immediately.**

Thrombosis

A blood clot in a vein (known as a 'venous thrombosis') can block the vein. This can happen in veins in the leg, the lung (a lung embolus), or other organs. A blood clot in an artery (known as 'arterial thrombosis') can block the artery. For example, a blood clot in an artery may cause a heart attack, or in the brain may cause a stroke.

Using any combined hormonal contraceptive increases a woman's risk of developing such clots compared with a woman not taking any combined hormonal contraceptive. The risk is not as high as the risk of developing a blood clot during pregnancy. The risk with progestagen-only methods like Nexplanon, is believed to be lower than in users of Pills that also contain oestrogens. There have been reports of blood clot formation like lung emboli, deep vein thrombosis, heart attacks and strokes in women using etonogestrel implants; however, available data do not suggest an increase in risk of these events in women using the implant.

If you suddenly notice possible signs of a thrombosis, you should see your doctor immediately. (see also "*When should you contact your doctor?*").

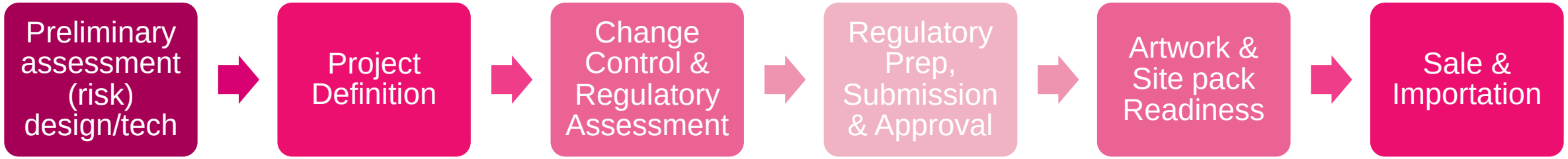
Other conditions

Menstrual bleeding pattern changes

Like with other progestagen-only contraceptives, your menstrual bleeding pattern may change when using Nexplanon. You may experience a change in frequency (absent, less frequent, more frequent or continuous), intensity (reduced or increased) or in duration. Absence of bleeding was reported in about 1 of 5 women while another 1 of 5 women reported frequent and/or

Artwork Leaflet

Overall E2E process Tech/CMC change from Artwork perspective



In which steps you are involved?

Where should labeling & artwork be assessed firstly?

Change Control & Regulatory Assessment

Module 3	Labeling	Artwork
• CMC docs • Ancillary • Stabilities	• Dosing • Administration	• Layout • Graphic Design

Does your company include Labeling & Artwork in the change control & Reg Assessment?

Regulatory Impact Assessments principles: Key for Compliance

Content (Labeling)

Distributer, Release, Manufacturing, Pack, API/DS Site changes:

- ✓ Markets enlist Sites in labeling components

Market sharing configuration changes:

- ✓ Changes in **SKU/Artwork shared packs** impact the content (adding/removing market content/language)

Material control strategy

- ✓ SKU proliferation vs extension (NDC/GTINS)

Other bundled changes:

- ✓ **Formulation** (excipients), **Embossing** (pictures shown in some artwork), **scoring** (divided doses), removing **non-marketed presentations** (dosing administrations), **graduations** (fractionated doses), etc

Technical & Design (Artwork)

Different Artwork technical drawings (Profiles):

- ✓ Dimensions, codes, batching areas, text orientations

Printing requirements :

- ✓ Color amount change, min. printable thickness line change

Graphic changes:

- ✓ **Printing style for foil** – random vs registered, **pre-printed vs printed in packaging line**, **anti-counterfeiting features** that are part of the graphic design like microtext and blemish points

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What is changing? (Content change)
Storage/Condition statement
Composition including salt forms, E-# and compendia designation, active ingredient, and excipients
Registration of drug product compendial compliance (e.g. update of China Registered Quality Specification - RQS)
Pack size/count Deliverable volume
Pack size presentation (e.g. 1 blister with 20 tablets vs 2 blisters with 10 tablets)
Drug Product manufacturer/ packager/ batch/ release/ MAH site name and location
Incompatibilities (dosing and administration)
Shelf-life
Container closure including fillers, desiccants, and dosing devices including removal, addition or change of a (co-packed) device.
Handling (e.g., reconstitution instructions and in use)
Embossing (image)/ Appearance/ Color/ Score line/ Markings /Shape/ Tablet dimensions
Deletion of strength including overages
Trademark
Drug Substance Country of Origin (source of API)
Instructions for Use (e.g. order of the tablets in the blister for products containing different composition of tablets among one primary packaging component)
Introduction or change of serialization, market barcode change (e.g. GTIN change, barcode change due to SKU number change)
Material type and material appearance for primary packaging component (e.g. aluminium vs PVC, transparent vs opaque)
Rearrangement of markets sharing the same packaging component (e.g. deletion, reallocation to different packing line – market A and market B share the same packaging component and there is change due to decision to assign market A to pack line Z and market B to pack line X)

What is changing? (Technical change)
New profile**
Change in current profile** (e.g. dimensions, technical codes, batching area, text orientation etc.)
Printing requirements (e.g. colour amount change, min. printable thickness line change etc.)
Graphic change (e.g. printing style for foil – random vs registered, pre-printed vs printed in packaging line, anti-counterfeiting features that are part of the graphic design like microtext and blemish points etc.)

Ultimate question is: when, where & how do we need to submit to Health Authority?

Do we need artwork mock-ups?

Do you obtain this outcome from your change control?

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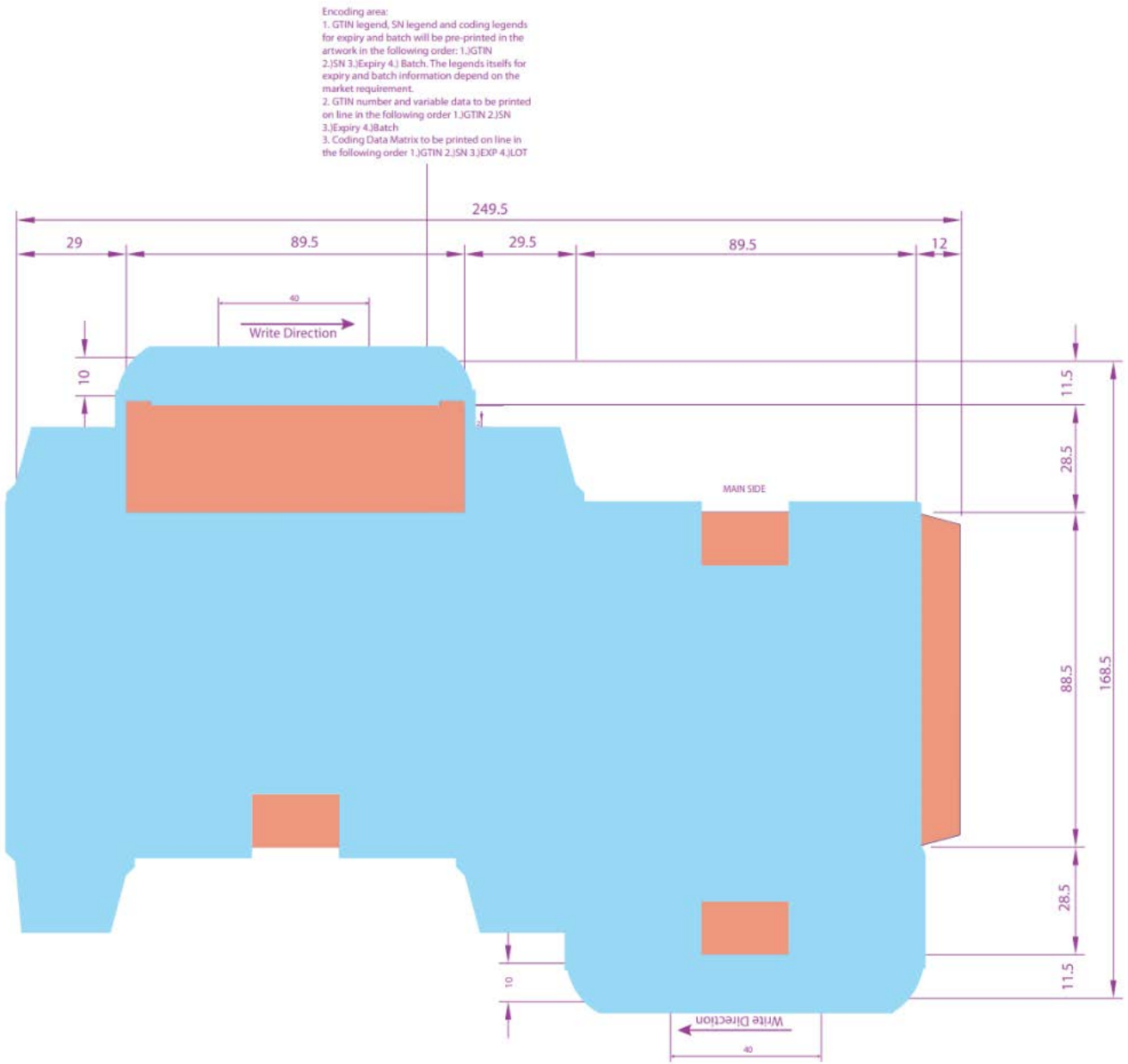

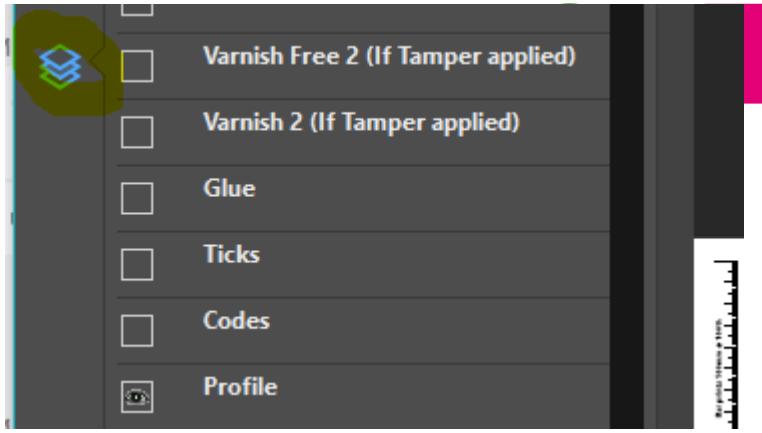

Example of Artwork Profile or Technical Drawing

Pre-Requisite to start mockups or production

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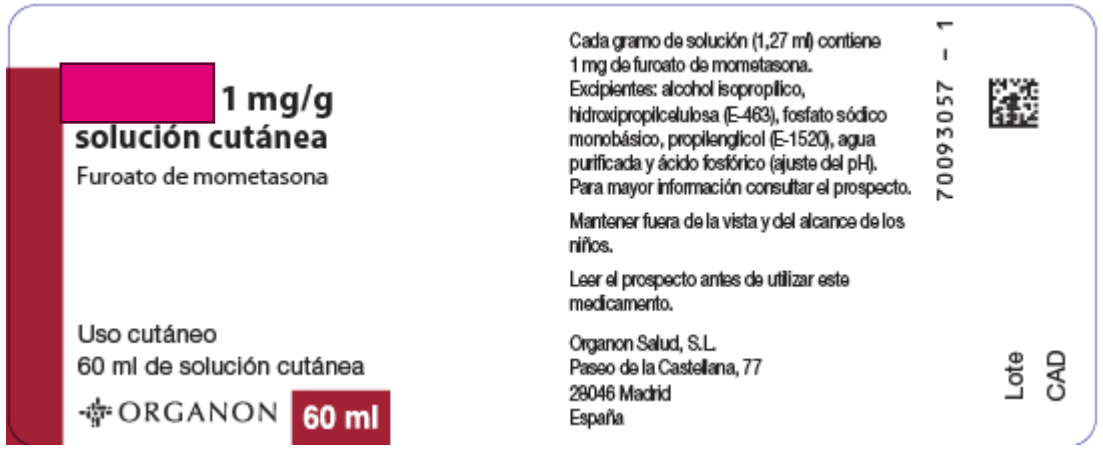
Here for her health

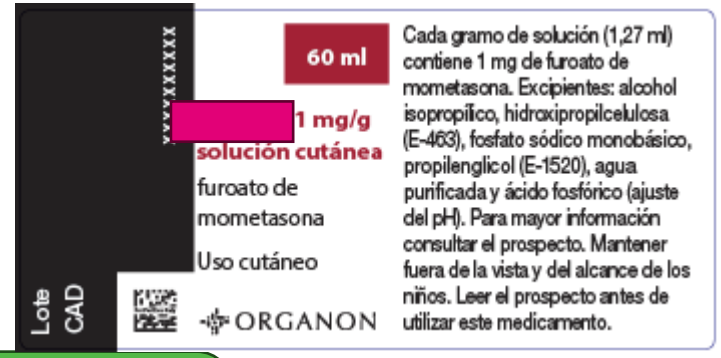
Example Site transfer - current label in current Site vs label in new Site

Content Readability

Current Packaging Site



New Packaging Site

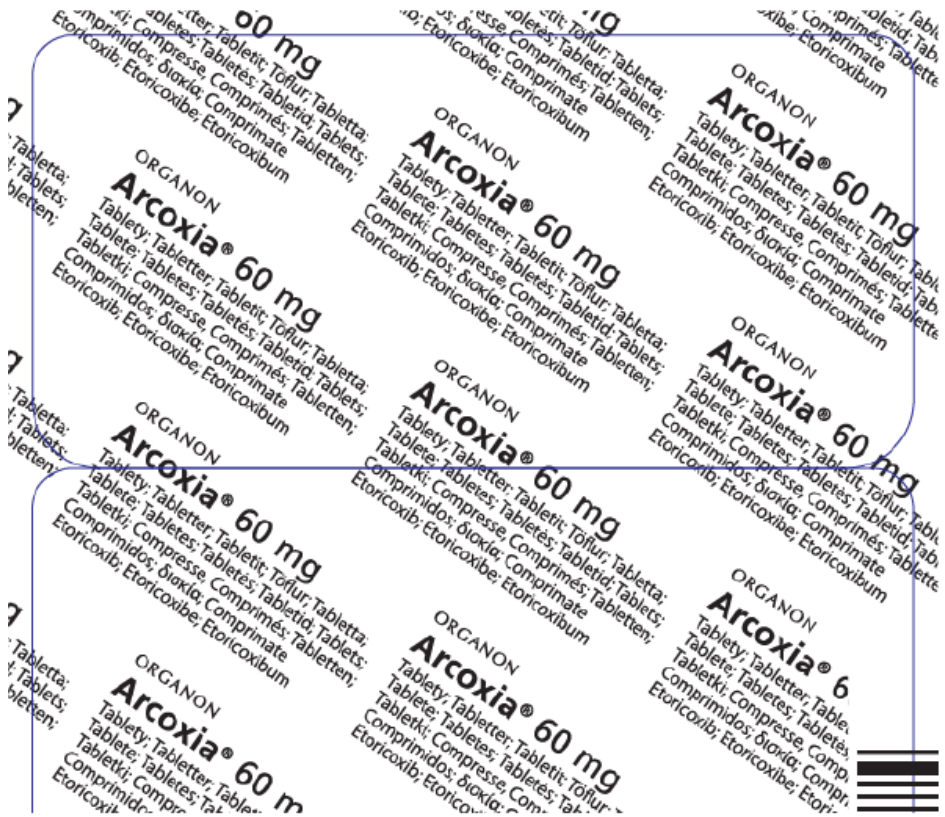


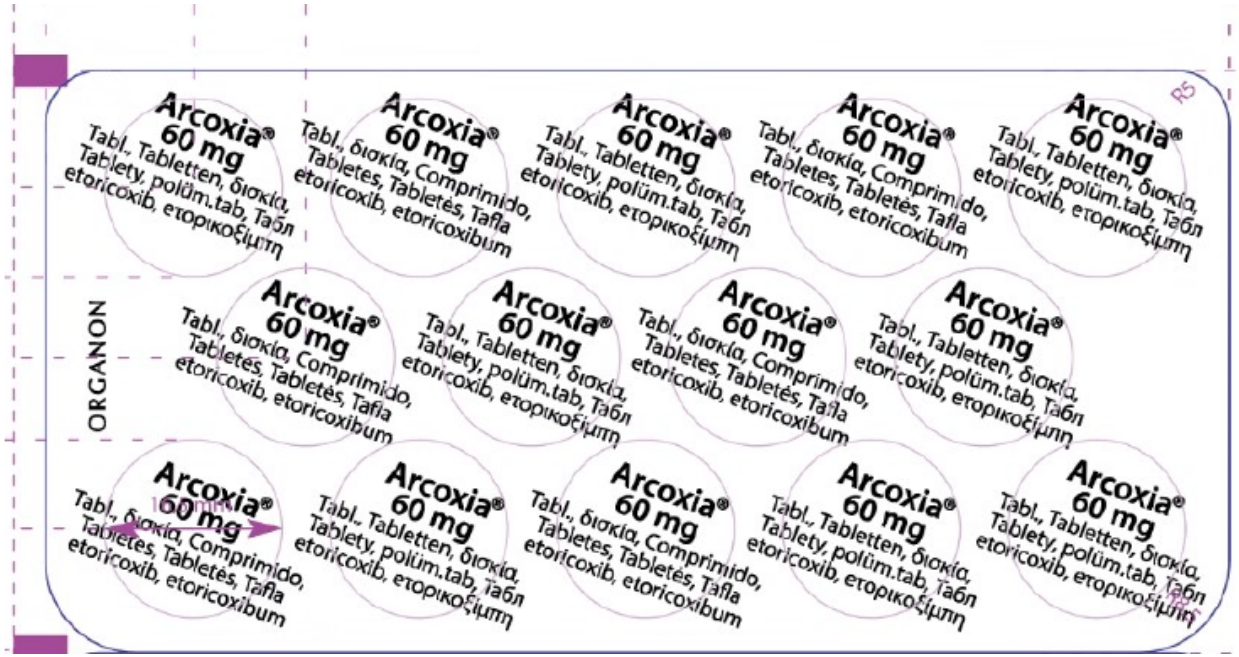
Who does this in your Company?

Change in dimensions from **50.8x125.4 mm** to **39x80 mm** require following actions to fit the content in the new label:

- **Major change** in the position of text and graphic elements
- **Reduction of the font size** for the main information (product name, strength, pharmaceutical form)
- **Removal** of the company address
- **Removal** of the spaces between the text sections
- **Removal** of the repeated information about fill size and pharmaceutical form
- Removal of graphic element

Examples of HA request





Thank you

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