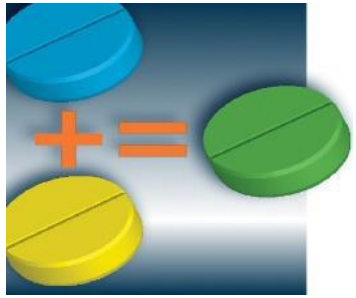

COMBINAZIONI A DOSE FISSA DI FARMACI: ASPETTI CLINICI, FORMULATIVI E REGOLATORI

*Combinazioni terapeutiche a dosi fisse: dal **dossier farmaceutico** all'Autorizzazione all'Immissione in Commercio*

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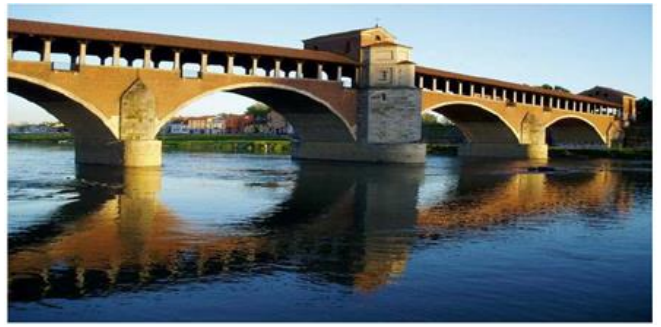
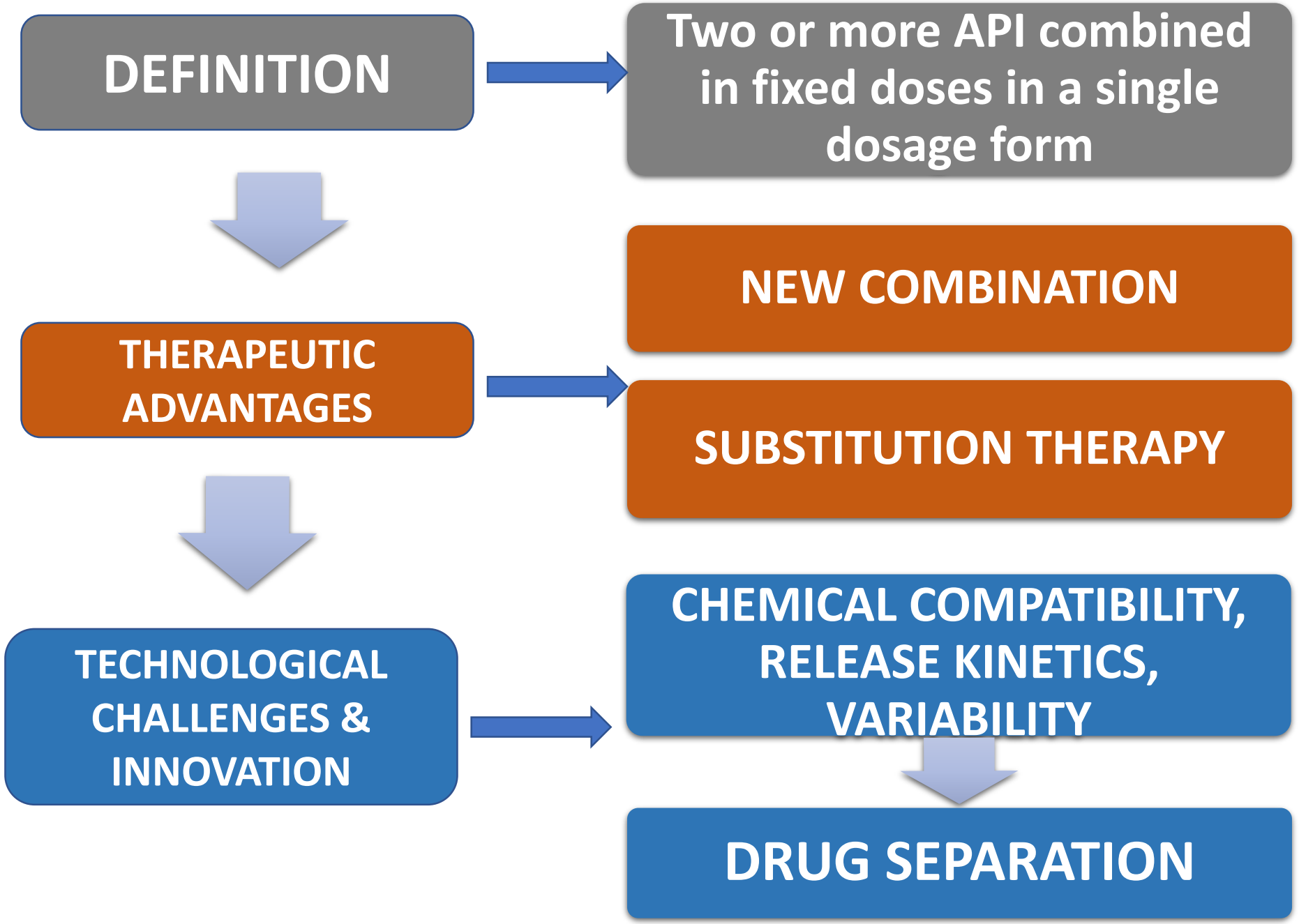
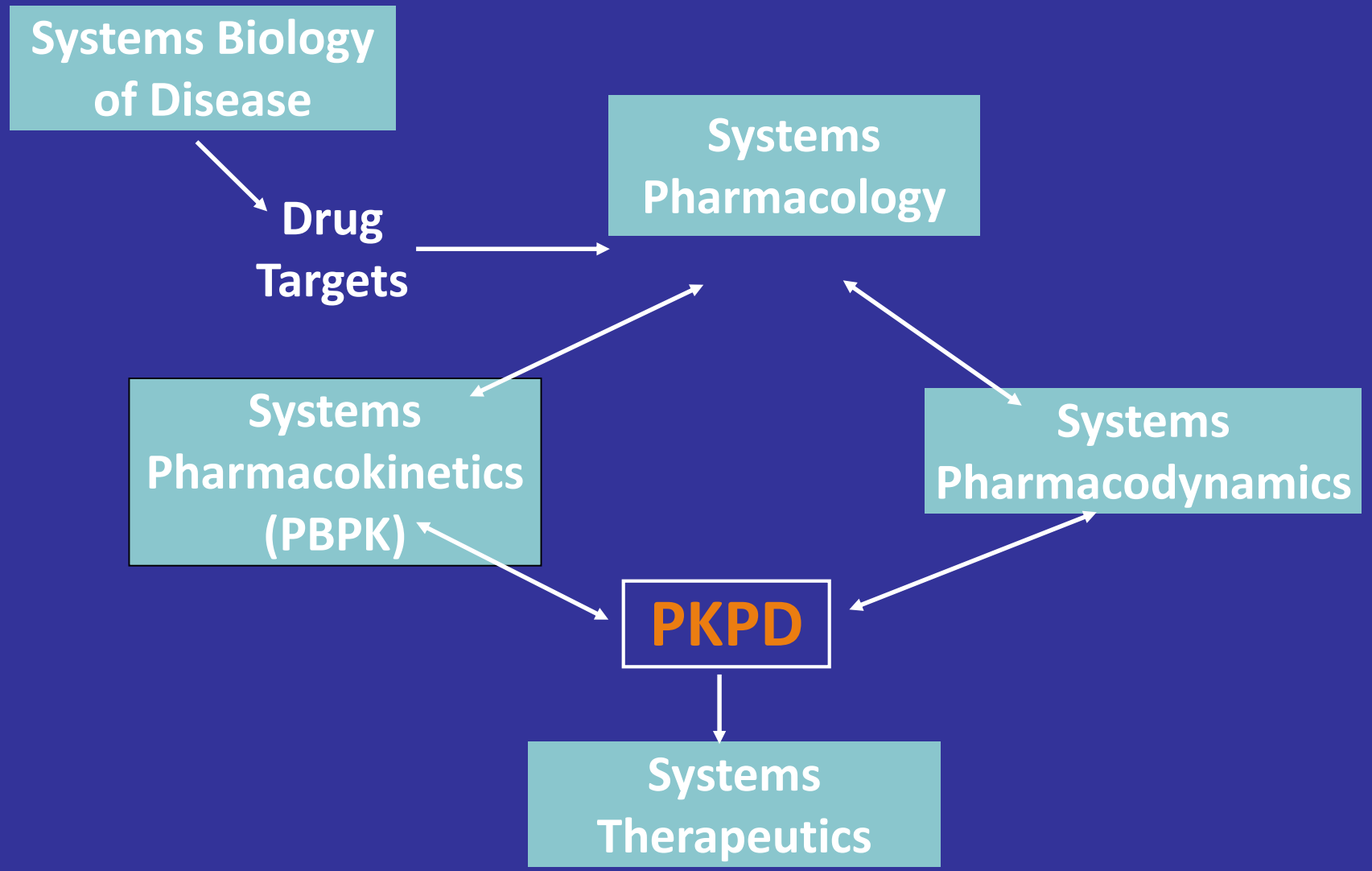



DEFINITION
Two or more API combined in fixed doses in a single dosage form
THERAPEUTIC ADVANTAGES
NEW COMBINATION
SUBSTITUTION THERAPY
TECHNOLOGICAL CHALLENGES & INNOVATION
CHEMICAL COMPATIBILITY, RELEASE KINETICS, VARIABILITY
DRUG SEPARATION



→ *Multitarget Drugs*

→ *Rational Single Target Drug Combinations*

Guidelines

- 1. Guideline on ***clinical development of fixed combination*** medicinal products, CHMP/EWP/240/95 Rev. 1 (19 February 2009)
- 2. ***Concept paper*** on the need to revise the Guideline on the clinical development of fixed dose combinations of medicinal products regarding dossier content requirements, EMA/CHMP/779887/2012 (11 February 2013)
- 3. Guideline on ***clinical development of fixed combination*** medicinal products, EMA/CHMP/158268/2017 (23 March 2017)
- 4. Guideline on clinical investigation of medicinal products in the ***treatment of hypertension*** – 9.Fixed-dose combinations, EMA/CHMP/29947/2013/Rev. 4 (23 June 2016)
- 5. ……

❖ No ***specific guidelines*** are available for the fixed-dose combination related to quality issues, meaning that the existing guidelines apply to pharmaceutical development!

❖ What are the ***basic information*** needed and r***equirements*** to be fulfilled!?

From a regulatory perspective..

EMA/CHMP/158268/2017

The ***basic scientific requirements for any fixed combination medicinal product*** are:

1. Justification of the pharmacological and medical ***rationale*** for the combination.

2. Establishment of the ***evidence base*** for the:

a. ***relevant contribution*** of all active substances to the desired therapeutic effect (efficacy and/or safety);

b. ***positive benefit-risk*** for the combination in the targeted indication.

3. ***Demonstration*** that the ***evidence*** presented - if based on combined administration of separate active substances - ***is relevant to the fixed combination medicinal product*** for which the application is made.

From a regulatory perspective..

EMA/CHMP/158268/2017

The therapeutic scenarios in which fixed combination medicinal products may be used are as follows:

- ***Add-on treatment*** of patients insufficiently responding to an existing therapy with one or more active substances
- ***Substitution therapy*** in patients adequately controlled with two or more active substances used in combination
- ***Initial combination therapy*** for patients receiving previously neither of the substance
- ***Additional requirements*** for development of fixed combination medicinal products with new active substance(s) (NAS)

Systems therapeutics poses new challenges and promotes innovation in drug delivery

Drug combinations →

- differences in the delivery rate of each separate compound may be needed, based on PKPD data
- Flexibility needed to cope with different dose ratios and with intersubject variability

Guidelines

- 1. Guideline on clinical development of fixed combination medicinal products, CHMP/EWP/240/95 Rev. 1 (19 February 2009)
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- 5. ……

❖ No ***specific guidelines*** are available for the fixed-dose combination related to quality issues, meaning that the existing guidelines apply to ***pharmaceutical development***!

❖ What are the ***basic information*** needed, the ***possible strategies*** and other r***equirements*** to be fulfilled!?

Nuova combinazione di ***nuova DS (NAS)*** con *DS nota* oppure di due *DS note*

Problematiche legate alle DSs

- ***Completa caratterizzazione DS nuova***
- Solubilità in fluidi biologici pH 1-8
- Stabilità, ev. stabilizzazione
- Strategie per solubilità/dissoluzione

Amorfizzazione, effetto tampone, …

Possibile introduzione di un sale e/o intermedio

- ***Differente BCS class delle sostanze***
- Differenze di ***dosaggio***
- ***Compatibilità*** chimica e fisica con gli eccipienti

Forma di dosaggio e sviluppo formulativo

- ***Compatibilità*** della miscela delle DSs
- Necessita di ***granulazione separata***

Es. instabilità/scarsa solubilità di una DS

- Eventuale ricorso a ***doppia compressione*** (bi-strato) o ***doppia incapsulazione***
- Ricorso a forma ad ***unità multiple***

Es.: minicompresse +granuli/pellets in capsule

Nuova combinazione di ***nuova DS (NAS)*** con *DS nota* oppure di due *DS note*

Sviluppo farmaceutico

- Necessità di introdurre un ***intermedio*** di processo e relativo controllo
- Necessità di sviluppare ***diverse formulazioni*** (es con un sale o una dispersione solida) ***della nuova DS***
- Necessità di ***diversi dosaggi della nuova DS*** da somministrate in combinazione libera
- Necessità di produrre ***diversi rapporti*** della combinazione fissa ***(strengths)***
- Necessità di ***bridging fra le varie formulazione usate nei trial clinici***

Sviluppo biofarmaceutico e clinico

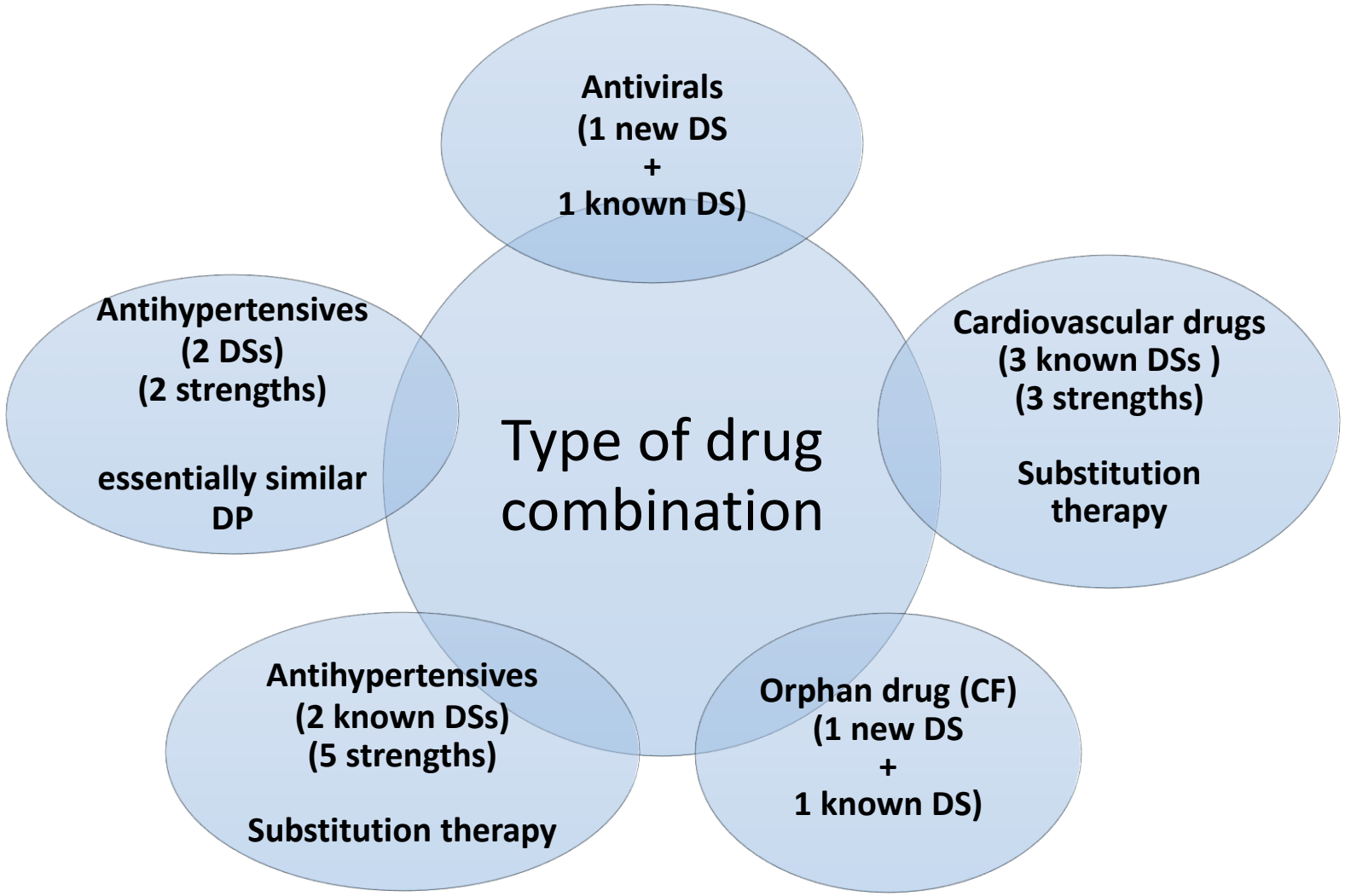
- Messa a punto/disponibilità di ***un test di dissoluzione validato e discriminatorio*** per entrambi le DS
- Se necessario mettere a punto ***un doppio test di dissoluzione*** per rispettare le condizioni di sink (diverse solubilità nei mezzi fisiologici)
- ***Biowaiver*** per ***diversi dosaggi (strengths)***, laddove applicabile

❖ ***Sviluppo clinico completo***

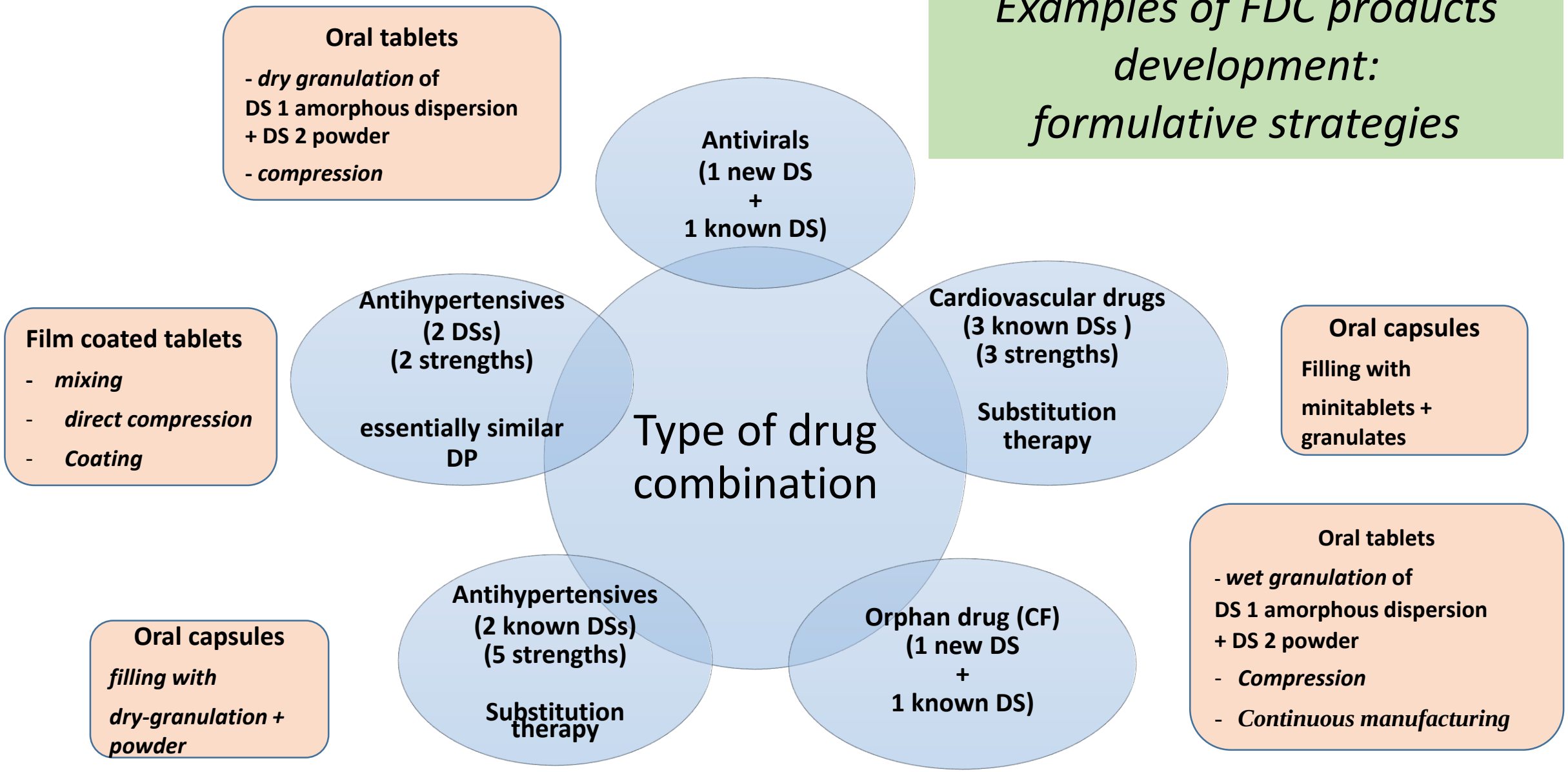
❖ Studi di ***bioequivalenza***

.

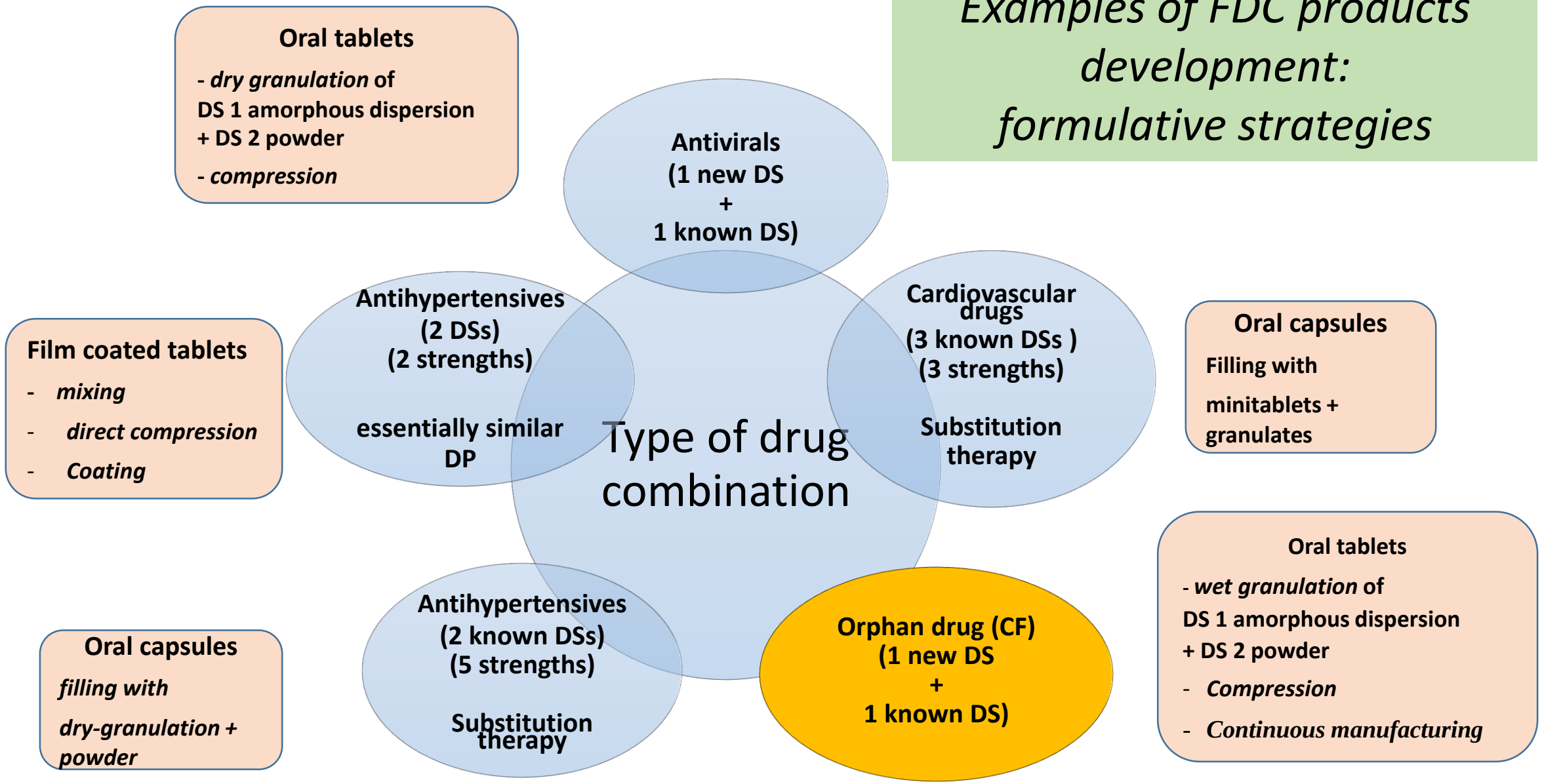
Examples of *fixed-dose combination (FDC)products*



Examples of FDC products development: formulative strategies



Examples of FDC products development: formulative strategies



New combination: new DS 1 (NAS) plus known DS 2 (one strength 200/125 mg) developed as ***orphan drug***

Drug substance 1

Appearance	White to off-white crystalline solid
pK_a-value:	***2.51 (basic) and 4.28 (acidic) at 25.0°C***.
Melting point	206 °C (DSC)
Partition coefficient:	log D is 2.29 at pH=7.4 and 25°C
Hygroscopicity:	Non-hygroscopic
Stereochemistry:	None
Polymorphism	Present. Form I and Form II are enantiotropically related (T_t=58-62°C) with Form I being the thermodynamically more stable above transition temperature. ***Fom I is used in clinical trials.***
Solubility (at room temperature and after 24 hours)	***Form I practically insoluble in water and buffer solutions pH 1.0 to pH 8.0*** sparingly soluble to freely soluble in process relevant solvents

Drug substance 2 *

Appearance	White to off-white crystalline solid
pK_a-value:	***9.40 (acid) and 11.60(acid) at 24.8 – 25.0***°C
Melting point	292°C
Partition coefficient:	log D value is 5.68 at pH=7.4 and 25°C
Hygroscopicity:	Low (slight) hygroscopicity
Stereochemistry:	None
Polymorphism	Present. Mixture of two major crystalline neat polymorphic forms (B and C). Form C is the most thermodynamically stable form.
Solubility (at room temperature and after 24 hours)	***practically insoluble in the aqueous solvents tested at pH = 1.0 -7.0 (< 0.05 µg/mL)*** and also in fasted and fed simulated intestinal fluids. more soluble in organic solvents than in aqueous solvents

*Used as spray-dried amorphous dispersion in stabilizing hydrophilic polymer and wetting agent ***(intermediate)***

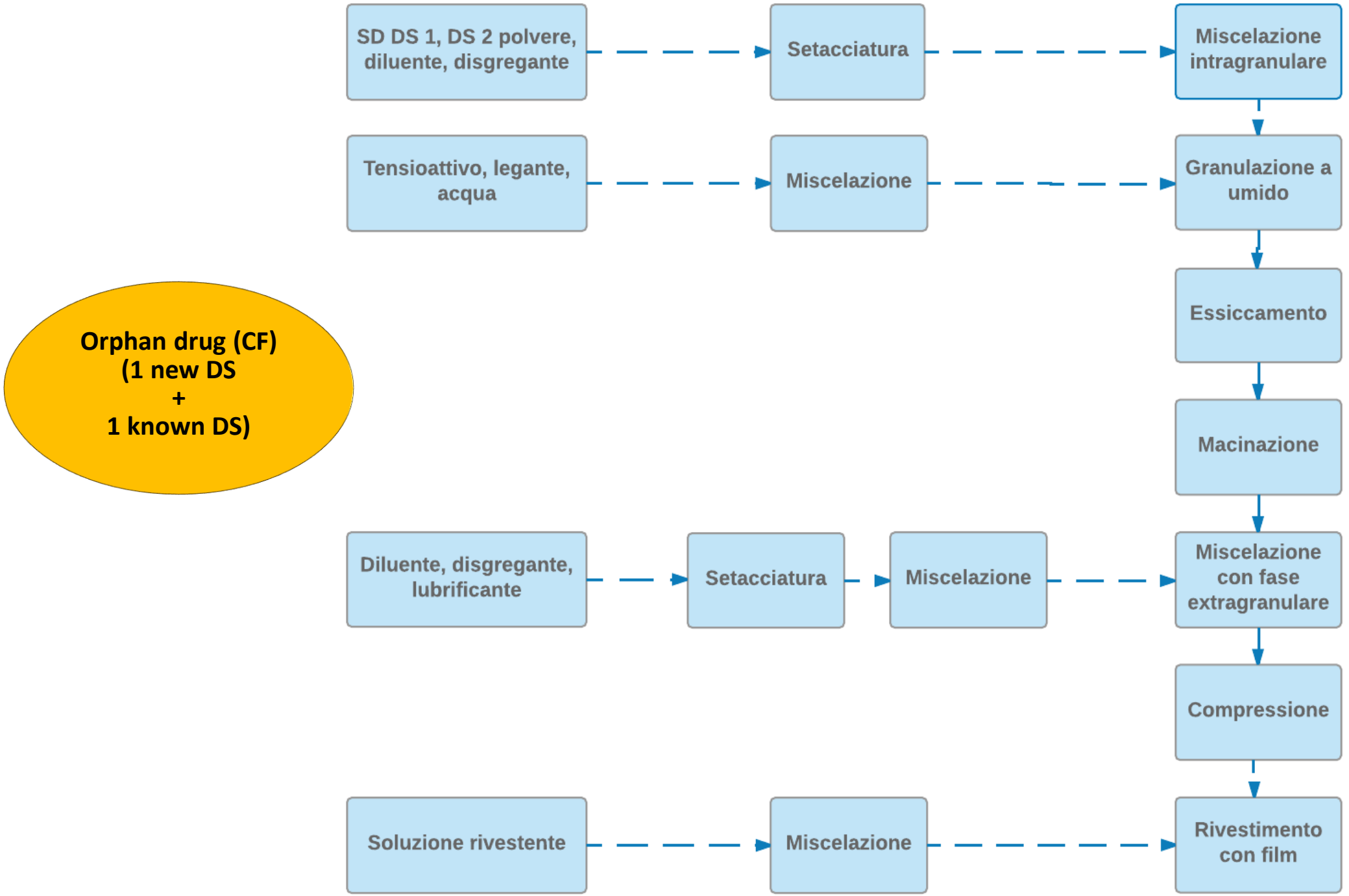
Pharmaceutical development

Step 1

- Desirable properties: ***immediate release oral dosage swallowable, acceptable shape and size,*** reliable drug product quality
- ***Initial*** development of an ***immediate release dosage form*** containing DS 1 (***suspension, capsule or tablet***) used in clinical trials
- ***DS 2 already available*** in suitable dosage form and used as ***SDD intermediate***
- ***Moving to combination therap***y new DS 1 formulations (eg smaller,…) are developed
- Then to enhance patient safety and compliance, ***a fixed dose combination*** DS1/DS2(FDC) (***200 mg/125 mg***) is developed
- no incompatibilities were detected between the two DSs, ***physical separation not required***

Step 2

- A FDC tablet is obtained using known excipients and standard mft processes (***wet granulation then compression and coating***)
- It is based on ***the same formulation*** (and process) used in monotherapy (a portion of DS 1 in the intra-granular blend was replaced by DS 2 ***keeping the ratio of the excipients the same***)
- a FDC tablet containing ***200 mg DS1 and 83 mg DS2*** was developed by changing the ratio of the drugs in the intra-granular blend, while ***keeping the ratio of the excipients the same***
- ***Bioequivalence*** demonstrated using either a fixed dose combination tablet (200 mg /125 mg) or individual tablets


Orphan drug (CF)
(1 new DS
+
1 known DS)
SD DS 1, DS 2 polvere, diluente, disgregante
Setacciatura
Miscelazione intragranulare
Tensioattivo, legante, acqua
Miscelazione
Granulazione a umido
Essiccamento
Macinazione
Diluente, disgregante, lubrificante
Setacciatura
Miscelazione
Miscelazione con fase extragranulare
Compressione
Soluzione rivestente
Miscelazione
Rivestimento con film

Pharmaceutical development

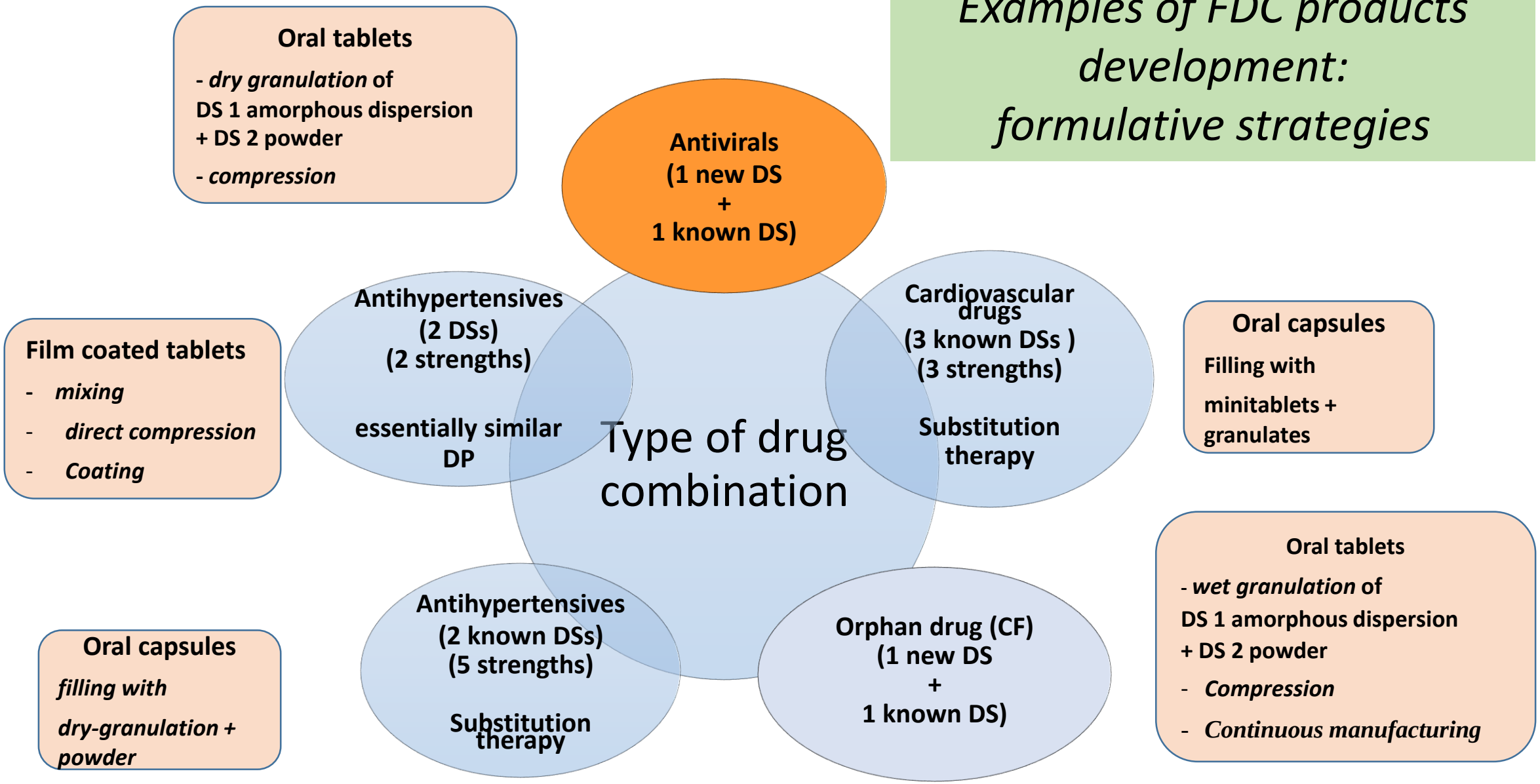
Dissolution test dvl

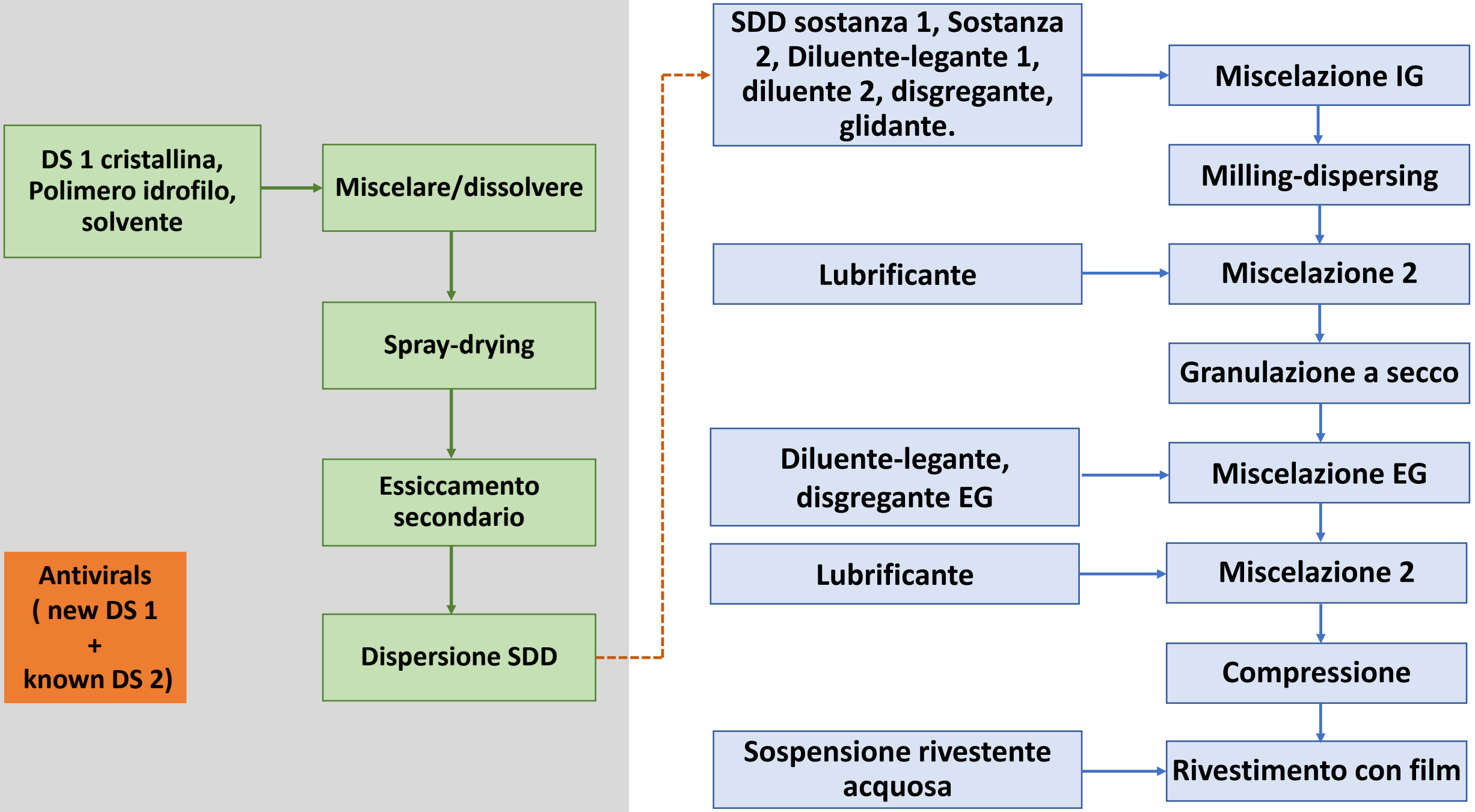
- ***Two independent in-vitro dissolution methods***, one for each active ingredient, were developed for testing both the FDC tablet, 200/125 mg and the FDC tablet, 200/83 mg.
- ***The dissolution of DS 1*** from the FDC tablets is determined using a medium of 0.5% cetyltrimethylammonium bromide (CTAB), pH 4.5 in Ph.Eur. 2.9.3 apparatus 2
- ***The dissolution of DS2*** is determined using 0.4% sodium lauryl sulfate (SLS), pH 6.8 also in Ph.Eur. 2.9.3 apparatus 2.
-

Manufacturing process dvl

- Intensive implementation of QbD
- Spray-drying of DS 1/polymer/surfactant mixture solvent solution
- Blending with DS 2 (micronized) and excipients
- Wet granulation (screw granulator)
- Drying in fluid bed drier
- Second blending and compresion
- Continuous manufacturing and extensive PAT

Examples of FDC products development: formulative strategies




DS 1 cristallina, Polimero idrofilo, solvente
Miscelare/dissolvere
Spray-drying
Essiccamento secondario
Dispersione SDD
Antivirals (new DS 1 + known DS 2)
SDD sostanza 1, Sostanza 2, Diluente-legante 1, diluente 2, disgregante, glidante.
Miscelazione IG
Milling-dispersing
Lubrificante
Miscelazione 2
Granulazione a secco
Diluente-legante, disgregante EG
Miscelazione EG
Lubrificante
Miscelazione 2
Compressione
Sospensione rivestente acquosa
Rivestimento con film

Conclusione

rules of thumbs and lessons learned

- Sviluppare una formulazione ***semplice e flessibile*** specialmente se ***DS NAS*** e in ***fase clinica 1*** (ev cambio di dosaggio)
- Tenere come base ***la formulazione della DS nota*** specialmente se possibile accomodare la DS nuova (es dosaggio più basso) o viceversa
- Nell'aggiungere nuovi dosaggi o strengths della FDC considerare le conseguenze in termini di ***numero di studi di BE*** necessari per il bridging
- Se si tratta di una FDC per terapia di sostituzione ***(2 o + DSs note***), lo sviluppo farm. è avvantaggiato ma ***non sfugge alle problematiche di compatibilità, solubilità, stabilità, ..***
- problematiche di biowaiver per le ***diverse strengths***

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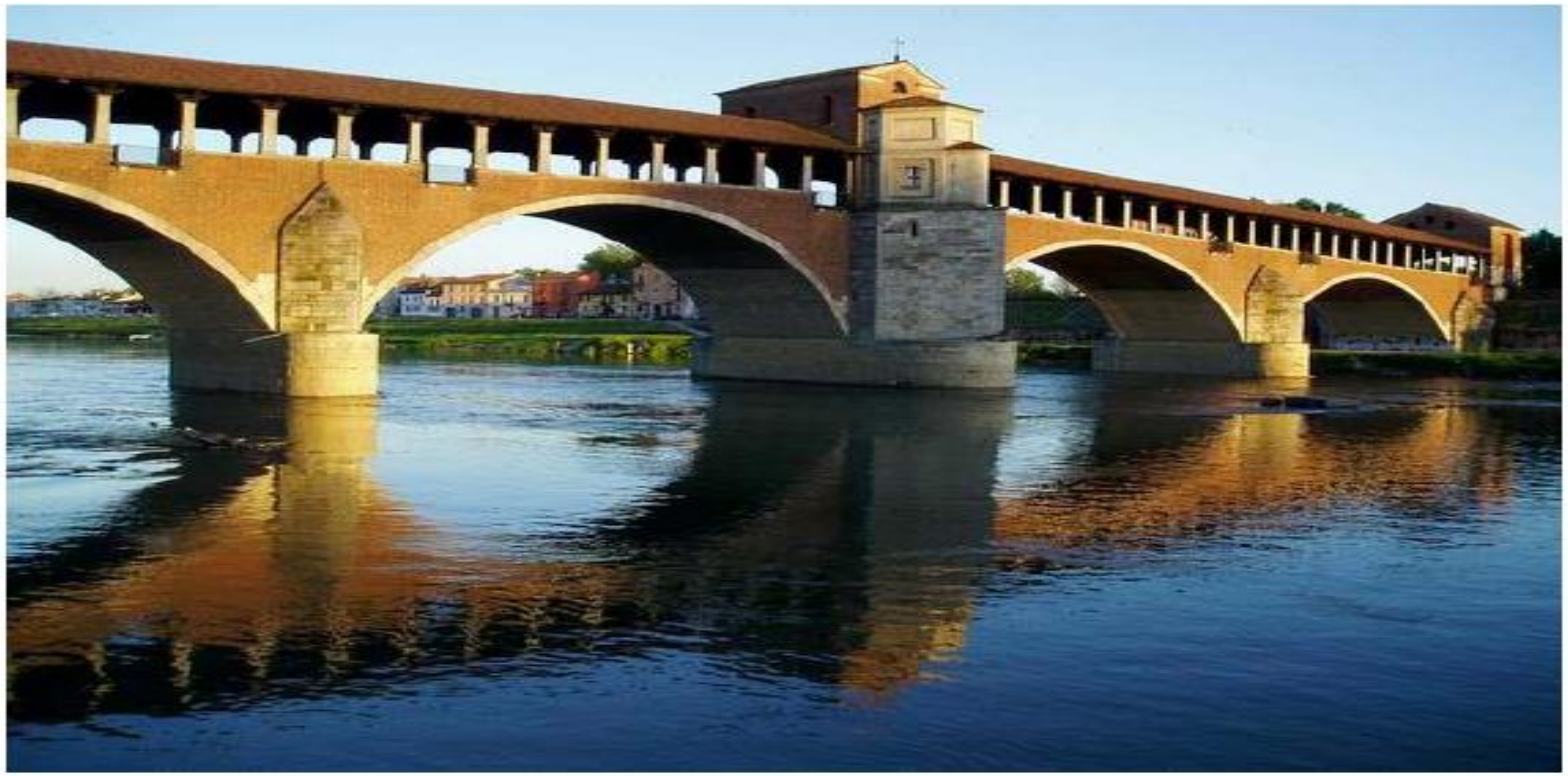

Grazie per l'attenzione