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Patient centered design in industrial drug development

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Current situation: How do drugs come into market ?

- Over decades mass-manufactured drugs («blockbusters») have been developed and developed for huge populations (e.g. key discoveries in the 1920s and 1930s such as insulin and penicillin, diazepam (Valium®) marketed in 1963 [1])

- Drug product development driven by broad applicability in huge populations, regulatory acceptance and manufacturing costs

- Little attention has been paid to specific patient populations (pediatric, elderly patients) until pediatric legislation was introduced in US/EU in the last 1-2 decades

- With the implementation of QbD in pharmaceutical development in the last decade (see annex to *ICH Q8 Pharmaceutical Development [2]),* it is now expected that *"...in all cases, the product should be designed to meet patients' needs and the intended product performance*"

How to implement patient-centricity in industrial drug development ?

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Patient-centricity (e.g. strong patient focus, acceptability testing in studies)

Overcome silos in company (e.g. clinical-CMC-functions)

Cultural company change (e.g. implement organisation elements with strong patient focus)

Adapt hiring and people development strategies to strengthen patient focus

The «design» of a new drug product....

QTPP = Quality Target Product Profile

Product description	Related to Patient centricity	Comments
Indication	Disease focus	-Age-specific requirements in terms of dosing flexibility ?
Route of administration/Dosing frequency	e.g. oral, parenteral	-Can be associated with age or patient specific requirements, e.g. swallowability/palatability -Sticking to a specific dosing regimen could be difficult for certain populations
Dosage form	e.g. film-coated tablet, softgel, hard capsule, pen for autoinjection etc.	- Could be critical with regards to size of dosage form, complexity (e.g. autoinjector)
Strength	Efficacy related	-Based upon clinical efficacy studies -Barely dose levels are monitored in older populations with reduced DMPK functionalities (safety in terms of over-/under-dosing)
Appearance	Product identification and quality aspects	- Should help to support compliance, avoid medication errors (colour, shape, size, imprinting)
Size	Product identification and complianace (beside technical requirements)	-Critical in case of too large dosage forms (swallowability)
Excipients	-Safety of patients	Certain excipeints represent challenge in specific patient populations

Examples of fields for improving patient centricity in industrial drug development

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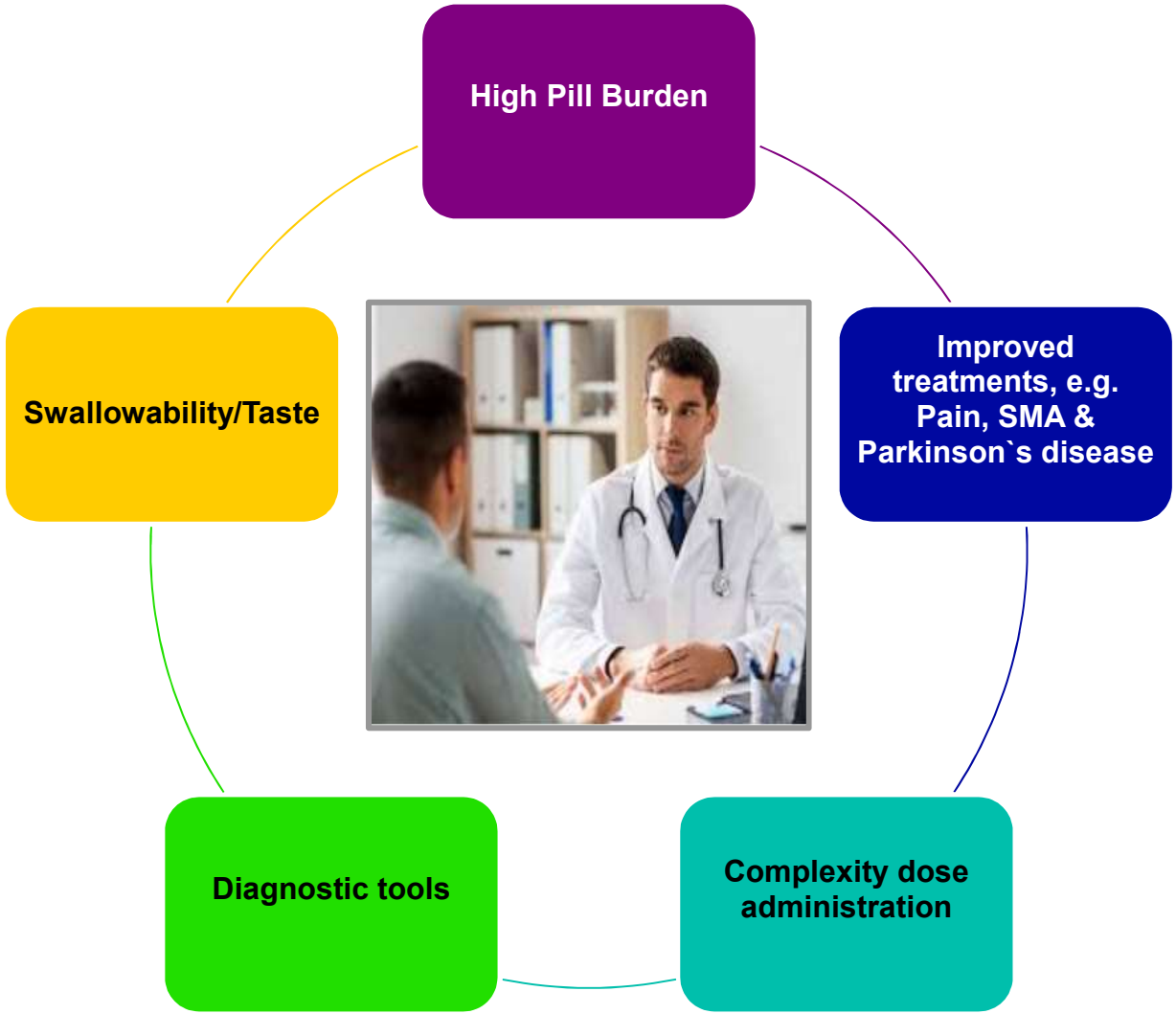
PATIENT CENTRICITY

DRUG PRODUCT DESIGN

CHALLENGES

- Pill burden, combina-tion with other drugs
- Complexity dose admini-stration, devices
- Swallowa-bility
- Communica-tion to patient (leaflet, videos, webpages)
- Improved safety, less toxicity, higher efficacy
- Diagnostic tools for better, individualt reatments

Examples how to improve patient centricity in modern drug development:



Easy to swallow alternatives

Figure 1: Illustrates mini-tablets and their different packaging configurations.

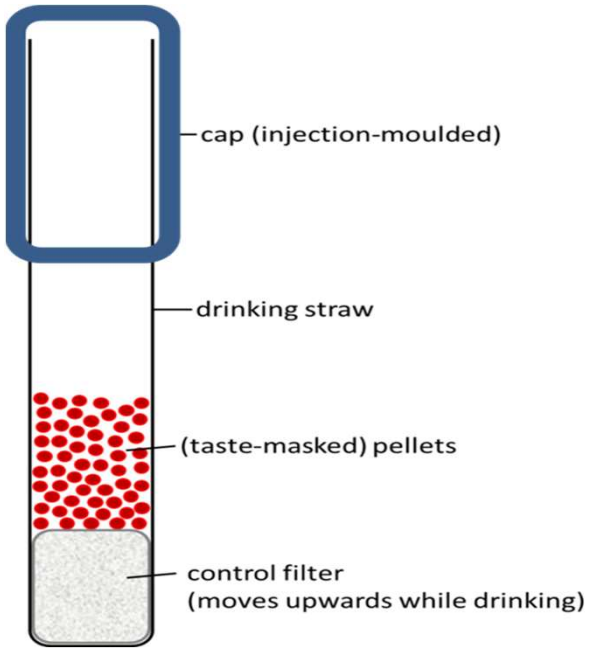
Multiparticulate dosage forms (Minitablets, Pellets)

- Powders, granules, pellets in sachets or capsules → 'sprinkling' with soft food (e.g. pudding) or in beverages (creating a suspension)
- FDA guidance: multi-particulates labeled for administration via sprinkling: size 2.5 mm, with no more than 10% variation over this to a max. size of 2.8 mm
- Typically for pediatric population, but also interesting for old population (e.g. Parkinson's disease, osteoporosis and phenylketonuria)
- GAP: Devices to dispense multiparticulates

Easy to swallow alternatives: Dose sipping technology using drinking straw for multi-particulates

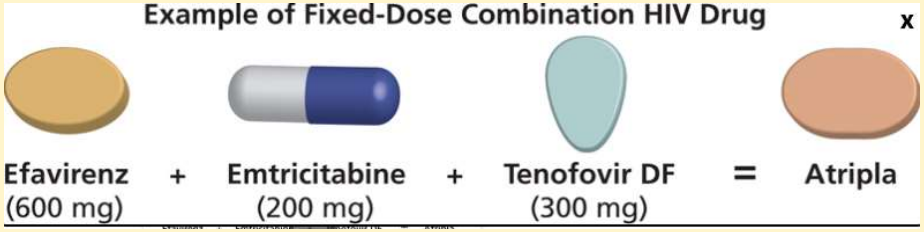
- Delivery system developed for pediatric population
- Houses dry medication in the form of film-coated, taste masked pellets
- Delivers a controlled dose (pre-dosing by the manufacturer) to the patient while enjoying its favorite drink

→ *avoids incorrect dosages, improves patient convenience and compliance*



Means to reduce *high pill burden* for geriatric patients

- Fixed dose combination drug products (FDCs)



- Long-acting active ingredients
- Sustained release/extended release formulations when appropriate (e.g. Accordion™ pill – see below)

- Alternative routes of administration (consider cost)

Improved treatment of diseases: E.g. Spinal muscular atrophy (SMA) with Evrysdi (home adminstration)

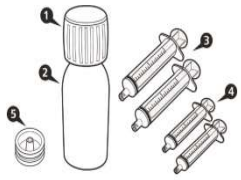


Figure A

Devices

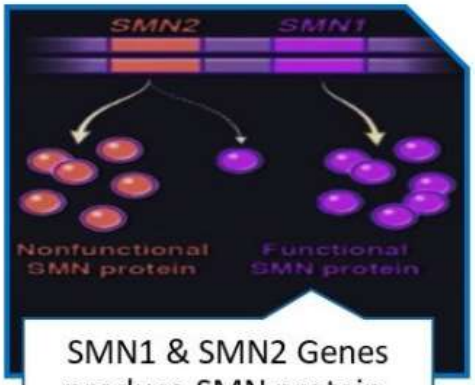
Evrysdi risdiplam

The first oral medicine in SMA which can be taken at home

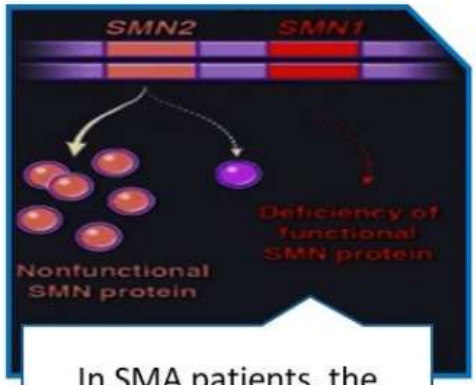
It is a daily oral dose can also be given through Gastrotomy-tube.

Indicated for children above 2 months & adults.

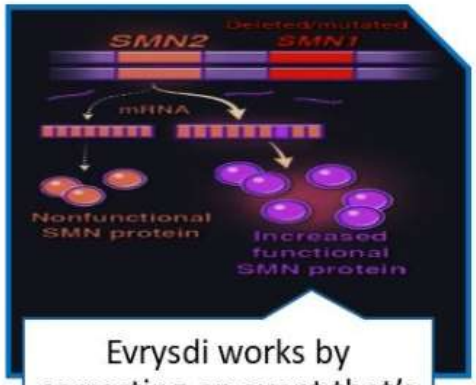
How Evrysdi works?



SMN1 & SMN2 Genes produce SMN protein. SMN1 makes functional SMN protein & SMN2 makes usually unstable protein



In SMA patients, the functional protein is almost less than10%, which leads to the motor neuron degeneration



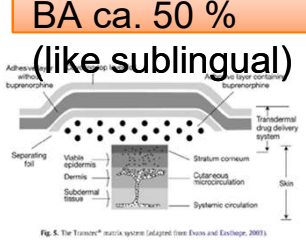
Evrysdi works by correcting an event that's called alternative splicing which allows the gene to make mature mRNA and final protein.

Improved treatment of diseases: E.g. Pain treatment (transdermal patch)

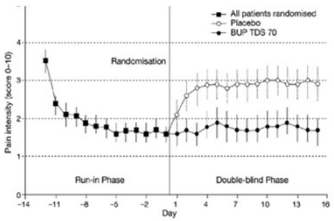
- Management of chronic pain (e.g. due to cancer) in geriatric patients is a challenge
- Several routes for Buprenorphin administration are available: parenteral (t1/2 2-3 h) oral (sublingual: > 24 h)
- Geriatric-friendly formulation: Transdermal patch
  - matrix with Buprenorphin (Transtec™ with 35, 52.5 and 70 µg/h available in Europe) allows for slow and steady release (e.g. up to 7 days)
  - damage does not cause dose dumping (t1/2 ca. 37 hours!), hepatic elimination (no close monitoring necessary in case of renal impairment)

. --> Reduced pill burden, patient convenience and compliance improved, safe application, different dosage strengths available

BA ca. 50 %
(like sublingual)



Pain reduction

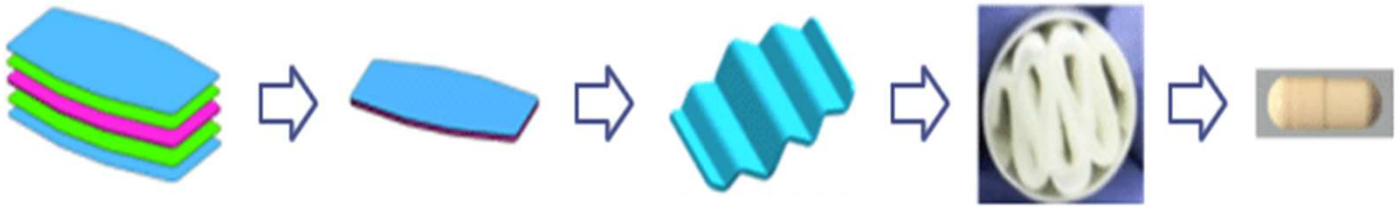


Source: Hans G. Kress, Clinical update on the pharmacology, efficacy and safety of transdermal Buprenorphine, European Journal of Pain 13 (2009) 219–230

Improved treatment of diseases: *E.g.* Parkinson`s disease

- Parkinson's disease (PD) is a progressively debilitating motor neuron disease: affects the dopaminergic neurons → characterized clinically by rigidity, resting tremor and bradykinesia (ca. 1 Mio patients in US)
- Levodopa = gold standard in PD treatment → peak plasma concentrations and bioavailability can be highly variable with a t1/2 of about 1 hour --> **short dose intervals**
- → important to reach stable plasma concentrations
  - Addition of carbidopa prevents peripherical conversion of LD to dopamine (increases LD in the bloodstream → more available to enter the brain + less side effects)
  - Controlled release: Accordion pill® ensures more stable plasma levels → better motor reponse (efficacy + patient convenience)

Unfolds in the stomach where it is kept forup to 12 h

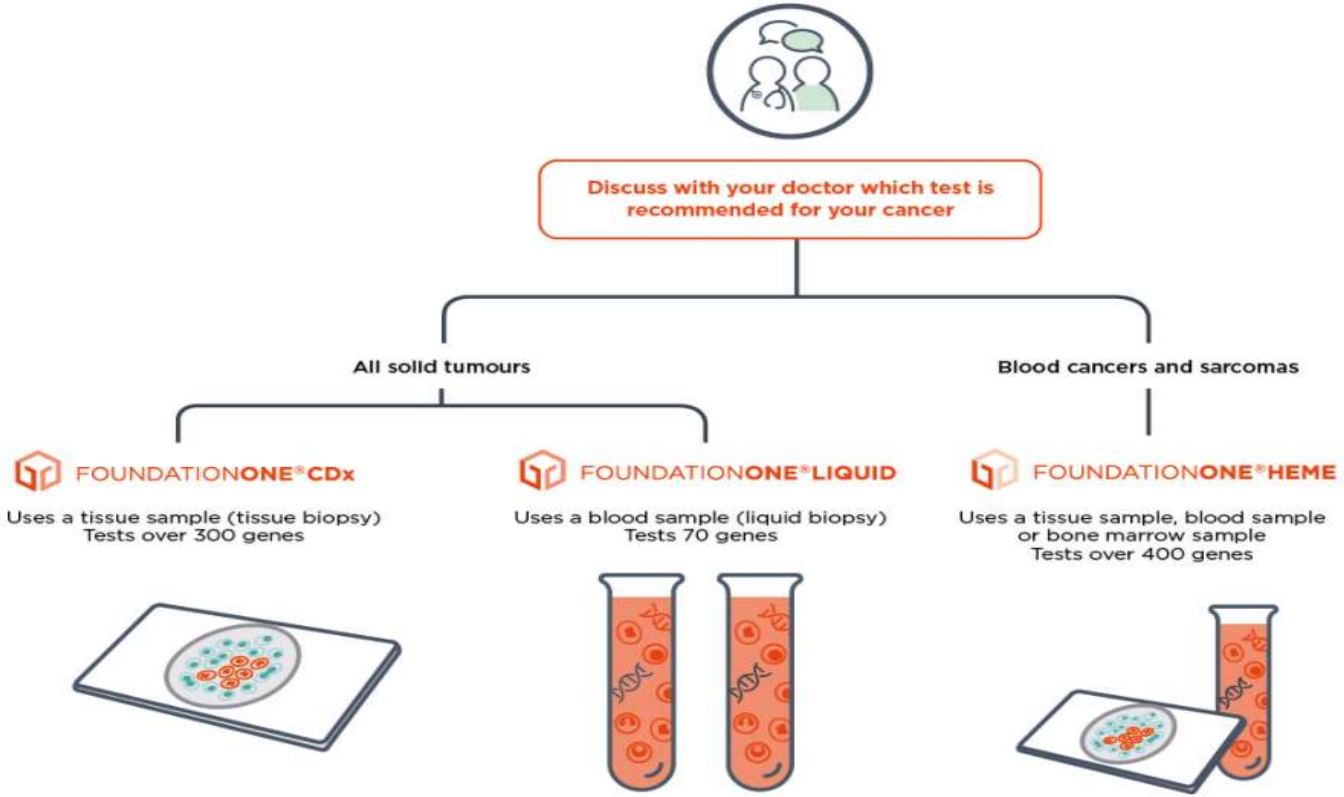


Releases Drug Substance in a controlled manner towards the upper part of the GI tract

Intec Readying for New Phase 3 Accordion Pill Study in Parkinson's

MAY 18, 2020 BY INES MARTINS, PHD IN NEWS.

Diagnostic tools: *Roche`s* FoundationOne Liquid CDx, a comprehensive pan-tumour liquid biopsy test

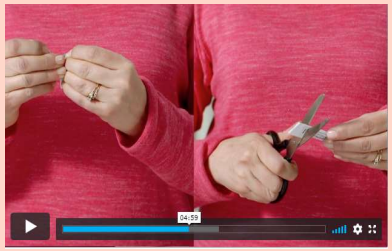
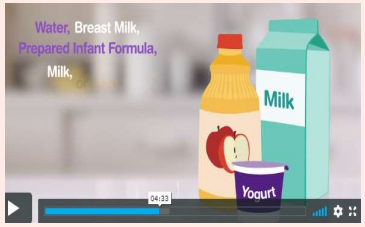
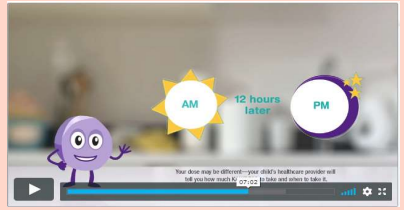


FoundationOne®CDx, FoundationOne®Liquid and FoundationOne®Heme search for multiple mutations in your cancer sample to increase your chances of finding a more precise treatment and help personalise your cancer treatment plan.[6–11,14–24]

Your care team will receive a comprehensive report including the details on your tumour profile as well as therapies and clinical trials for you to discuss together and help guide your treatment plan.[6–11,25]

Complexity of dose administration

- Improve caregivers life e.g. By using modern media/videos for drug administration – Example Kalydeco™ (cystic fibrosis)

Step 1: preparing all tools needed (sachet with granules, softfood, spoon)	Step 2: Opening sachet, mixing with softfood	Step 3: Administration to patient and instruction for caregivers when to take drug (prior or after meal, every 12 hrs)
		
		
		

Conclusion – gaps we need to close ?

- Patient centricity should become an integral part of industrial drug development from the very early stages onwards
- We need to evaluate much more the hurdles patients need to overcome in terms of drug administration and compliance (e.g. dysphagia in elderly patients, complexity to take the drug, pill burden, size of dosage forms)
- There is a need by patients for better medical devices to ease drug intake
- Further development of innovative diagnostic tools to individualize therapies and drug administration for the patients
- We need to improve our communication about therapies and drug administration for patients and caregivers

Doing now what patients need next