ONDANSETRON RAPIDFILM™:
AN INNOVATIVE PHARMACEUTICAL FORM TO IMPROVE PATIENT COMPLIANCE

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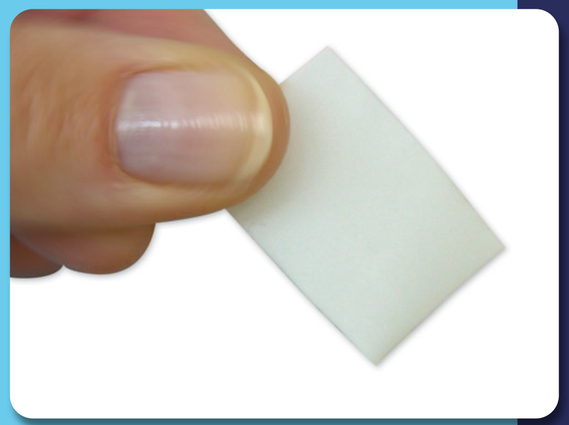
RAPIDFILM TECHNOLOGY



Flexible, thin film
Size: between 3 and 6 cm^2
Thickness: approx. 100 µm

RapidFilm™ technology, developed in joint venture by APR Applied Pharma Research SA and Labtec GmbH, is a novel, patented, non-mucoadhesive, fast dissolving, oral delivery system based on a water soluble polymer.
Placed on top of the tongue, the film disperses within seconds.
It is an orodispersible form complying with the Orodispersible Tablet definition of the European Pharmacopoeia, but, instead of compressing or lyophylizing, it is obtained by casting a polymer mass.

An active ingredient can be included in the film

BENEFITS OF RAPIDFILM TECHNOLOGY
as delivery system for MEDICINAL PRODUCTS

NO SWALLOWING DIFFICULTIES

Better patient compliance
It is estimated that 25% of the population find the swallowing of tablets and capsules difficult and therefore do not take their medication as prescribed, resulting in ineffective therapy.

IT CAN NOT BE SPIT OUT

Ideal for paediatric and geriatric use

NO LIQUID NECESSARY FOR INTAKE

“Take away“ medicine

VERY SLIM FORMAT

Can be carried in the wallet

RAPIDFILM TECHNOLOGY COMBINES THE BENEFITS OF LIQUID DOSAGE FORMS (easy administration) **AND OF SOLID DOSAGE FORMS** (exact secure dosing)

RAPIDFILM as delivery system for a KNOWN ACTIVE INGREDIENT: choice of ONDANSETRON as API

1. REGULATORY EVALUATIONS

PATENT EXPIRATION DATE for the API → already expired

REFERENCE PRODUCT → Zofran by GSK authorized in EU for more than 8 years

2. TECHNICAL EVALUATIONS

STRENGTHS of the Reference Product: within the feasibility range of RapidFilm technology → ok: 4 mg and 8 mg

3. MARKETING EVALUATIONS

COSTS of the Reference Product on the market → ok

Yearly SALES of the Reference Product → ok

4. CLINICAL EVALUATIONS

THERAPEUTIC ACTION → **MEDICAL NEED of this API delivered by a RAPIDFILM**

MEDICAL NEED of **ONDANSETRON** RAPIDFILM

Ondansetron is an inhibitor of 5-HT3 receptors, used orally, intravenously, intramuscularly or rectally for the prevention of nausea and vomiting associated with emetogenic cancer treatments.

Ondansetron RapidFilm™ was especially designed for higher patient compliance: considering the target population, who suffers of nausea and vomiting, it offers multiple competitive advantages versus the already marketed oral pharmaceutical forms of ondansetron:

vs Zofran Tablets

swallowing is easy and water is not needed

vs Zofran Syrup

no liquid intake and strawberry taste in the mouth, easier dosing accuracy, shorter handling time

vs Zofran ODT

easier to be handled, stored and taken away

the absence of Aspartame in the formulation makes the product safe also for phenylketonuric patients, for whom the use of Zofran ODT is contraindicated

DEVELOPMENT PLAN FOR **ONDANSETRON** RAPIDFILM

TECHNICAL DEVELOPMENT

CLINICAL DEVELOPMENT

REGULATORY DEVELOPMENT

STEP 1:
Technical Feasibility

STEP 2:
Pilot Bioequivalence Study

STEP 3:
Scale-up and Validation

STEP 4:
Pivotal Bioequivalence Study

STEP 5:
Preparation of the Common Technical Doc

Development Plan approved by BfArM, the German Authority, during a Scientific Advice

ONDANSETRON DEVELOPMENT

STEP 1: Technical Feasibility

Ondansetron RapidFilm™ prototype was developed in the laboratories of Labtec GmbH, Germany:

1. **Patent analysis and choice of the active substance's supplier**

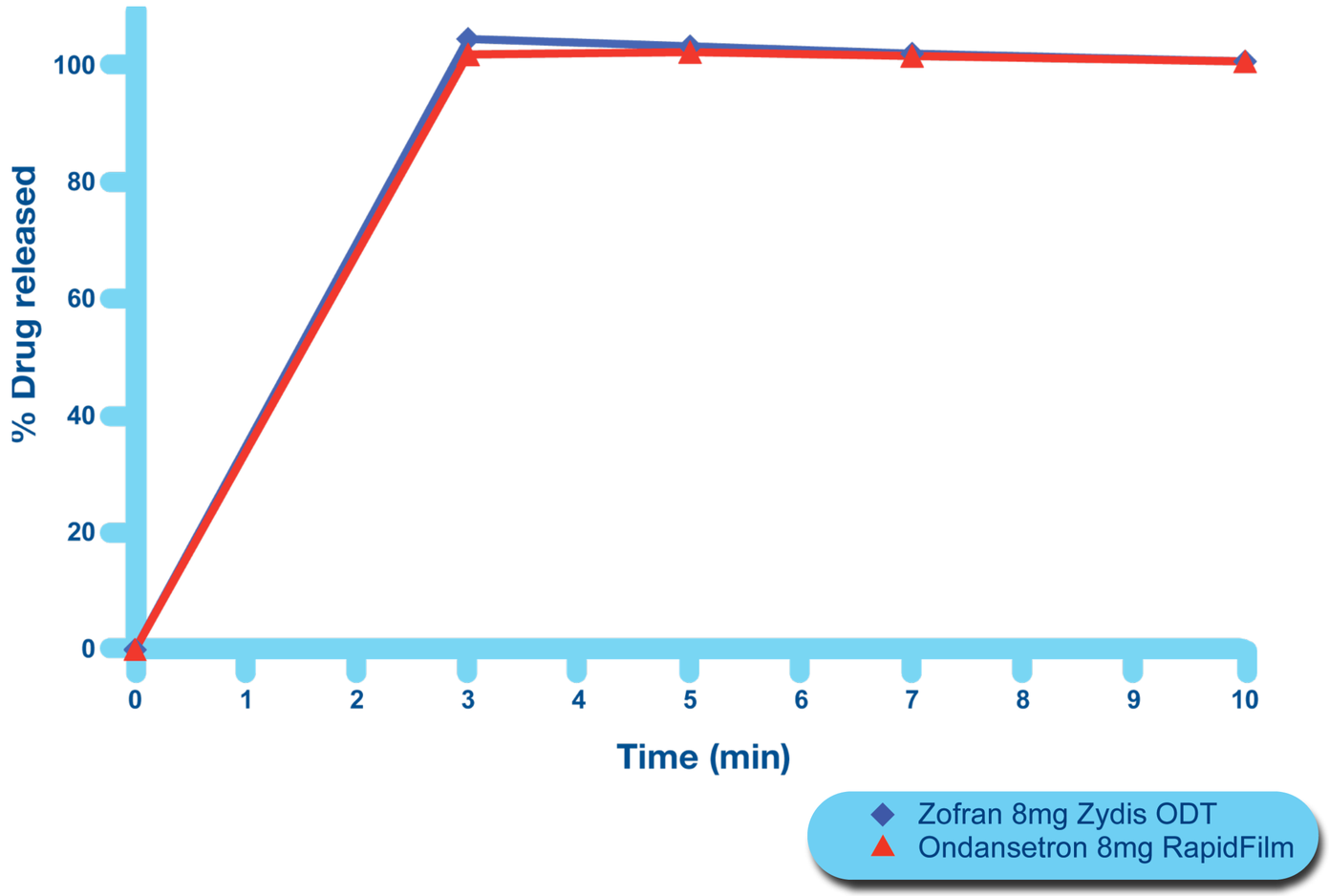
2. **Formulation study of Ondansetron in RapidFilm and preparation of some prototypes at laboratory level**

   A viscous and homogenous dispersion of the API and the excipients in volatile solvents is coated in a thin layer of defined thickness, on a carrier foil; after drying, when a solid flexible laminate is gained, by using a die, the final RapidFilms punched from the laminate.

3. **Determination of the in-vitro dissolution profile of the new prototypes and comparison with the Reference ones**

4. **Analytical method development and preliminary Stability Studies at ICH conditions**

5. **Selection of prototype for pilot Bioequivalence Study**

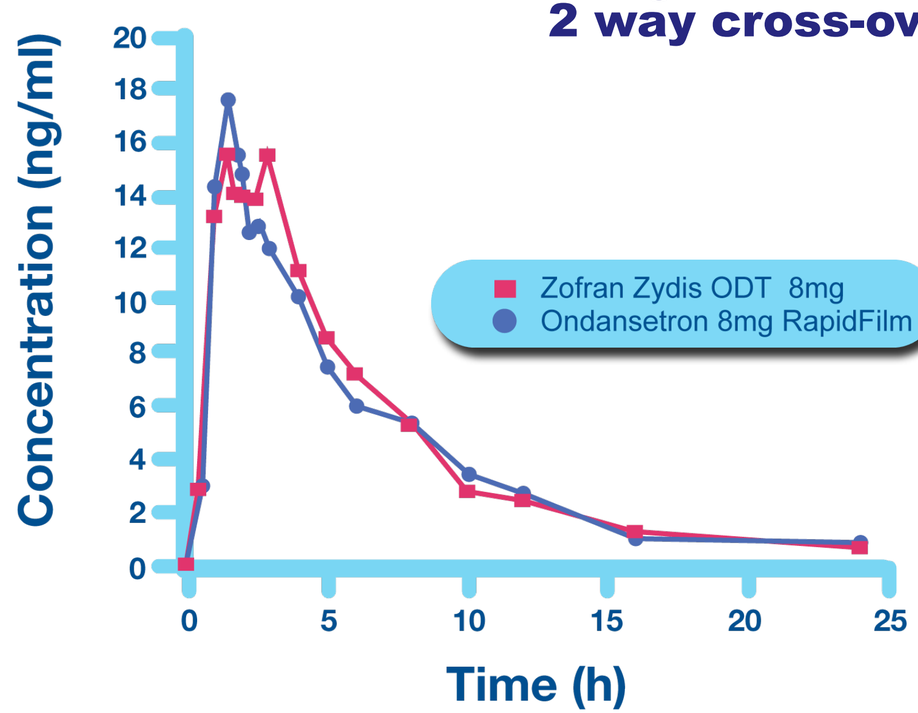


ONDANSETRON DEVELOPMENT

STEP 2: Pilot Bioequivalence Study

Design:
2 way cross-over on 6 volunteers

Treatments:
Ondansetron RapidFilm 8mg vs Zofran Zydis ODT (Germany) 8mg



	Zofran ODT	Ondansetron RapidFilm
AUC_{0-t} (ng/ml*h)	100.05	94.11
AUC_{0-inf} (ng/ml*h)	103.66	98.18
C_{max} (ng/ml)	20.37	18.75
T_{max} (h)	1.71	1.58

Test name	Parameter	Test value	Lower 90% CL	Upper 90% CL
Classic 90% CI	AUC0-t	96.32	82.87	111.96
Classic 90% CI	AUC0inf	96.79	83.81	111.78
Classic 90% CI	Cmax	91.84	72.64	116.13

R/T are bioequivalent for the extent of absorption
Reference interval [80% , 125%]

Cmax was quite out of the accepted 90% confidence intervals, but, based on statistician evaluations, the bioequivalence also for Cmax could be assessed by increasing the samples size to 24 subjects.
Reference interval [80% , 125%]

ONDANSETRON DEVELOPMENT

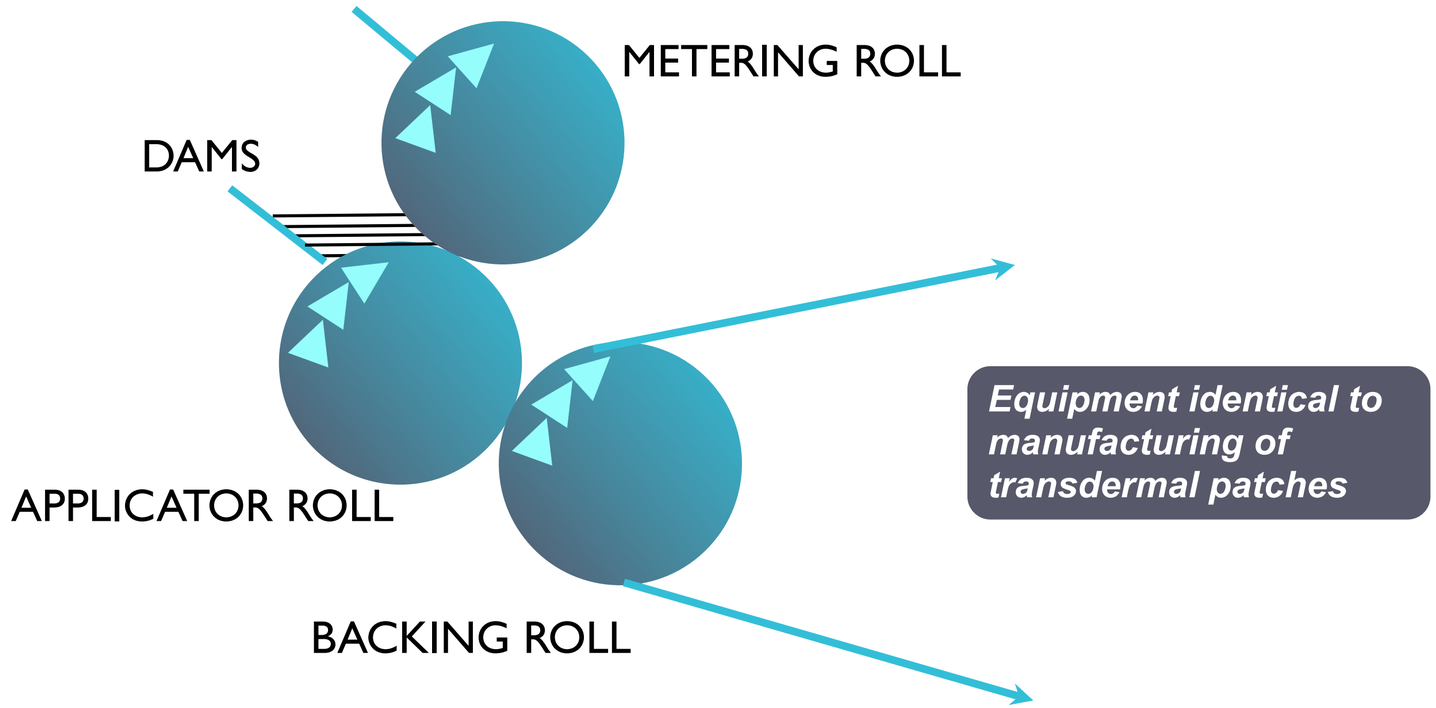
STEP 3: Scale-up and Validation

Ondansetron RapidFilm™ production scale-up and validation was developed in a GMP-certified facility

SCALE-UP:

-the process validation was performed on batches corresponding to the full commercial size, by punching the two dosage strengths (4 and 8 mg, sized 3 cm^2 and 6 cm^2 respectively) from each laminate.

-all analytical methods were validated, according to European Pharmacopoeia Specifications/ Requirements.



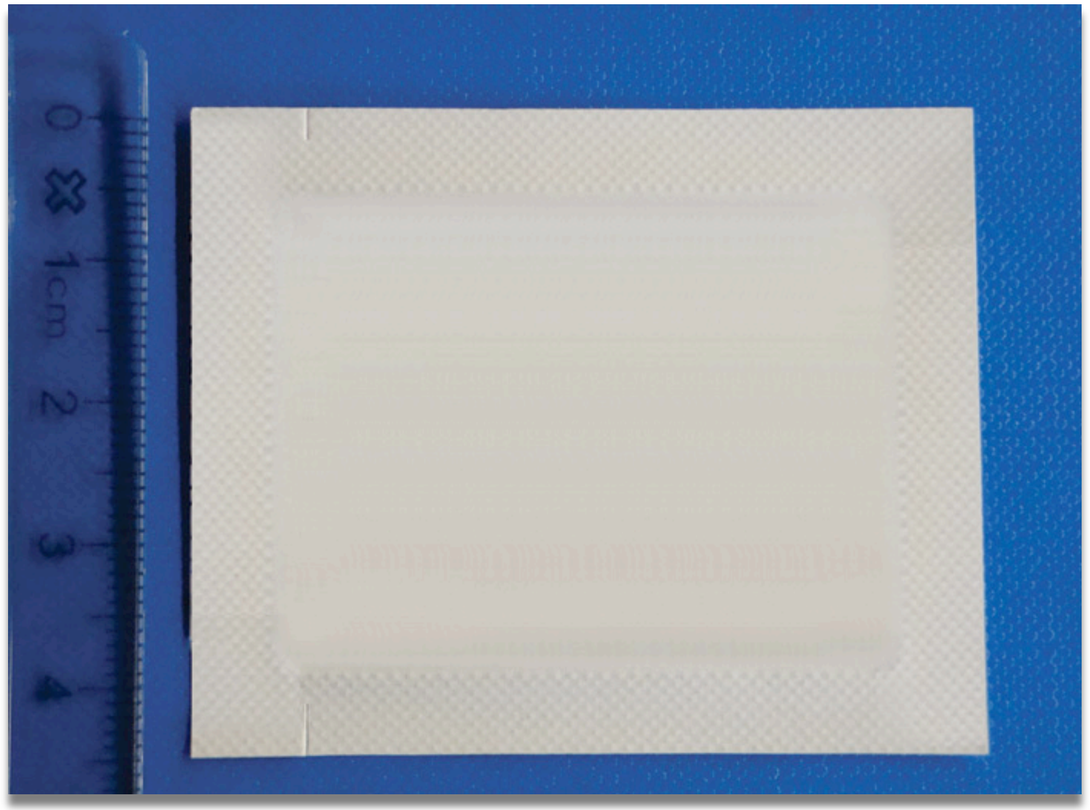
Equipment identical to manufacturing of transdermal patches

ONDANSETRON DEVELOPMENT

STEP 3: Scale-up and Validation

PACKAGING AND STABILITY:

Each RapidFilm™ is packed in a pouch, made of composite foil, which is opened and removed before application.
The formal stability testing was performed, according to ICH stability protocol.



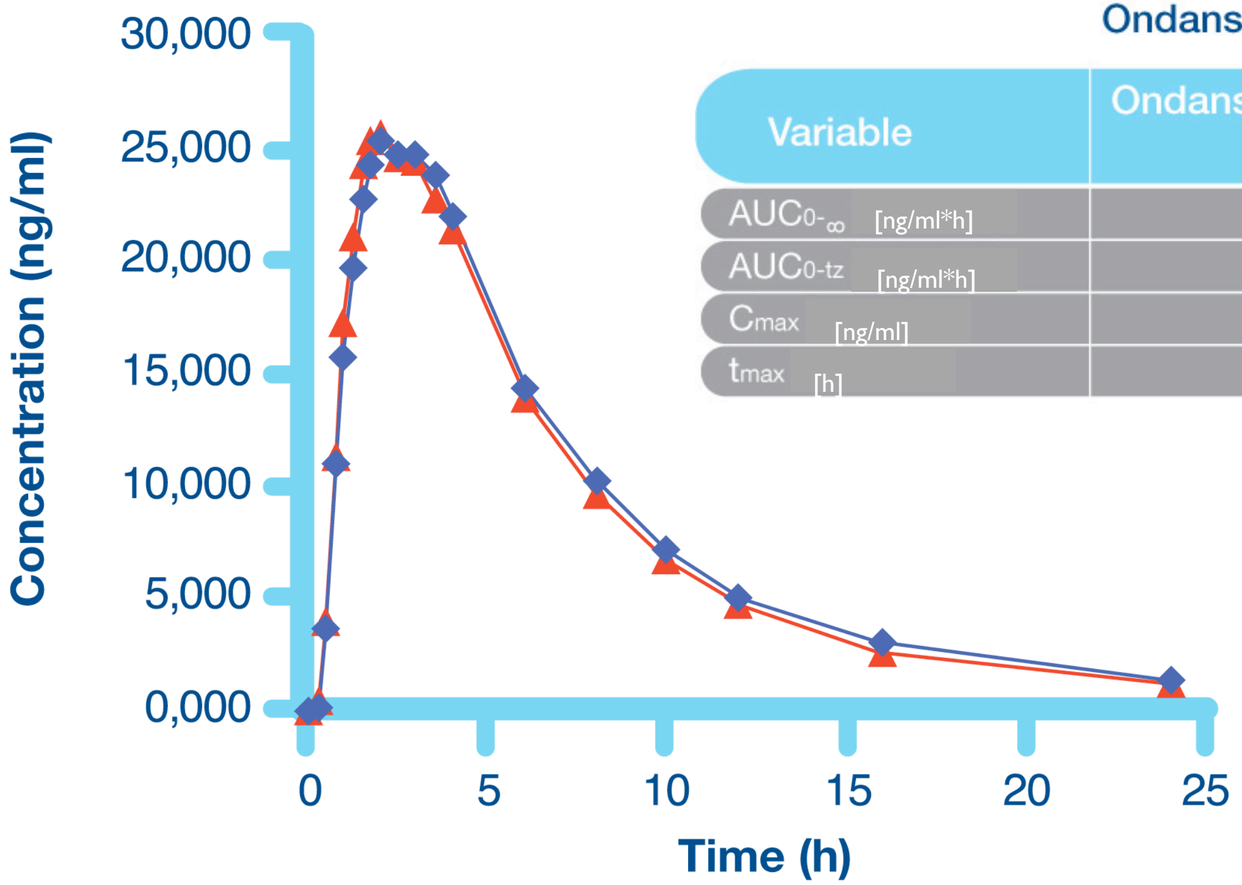
ONDANSETRON DEVELOPMENT

STEP 4: Pivotal Bioequivalence Study

Design:
2 way cross-over on 24 volunteers

Treatments:
Ondansetron RapidFilm 8mg vs Zofran Zydis ODT (Germany) 8mg

Mean concentrations:



Ondansetron - Summary Kinetic Variables

Variable	Ondansetron RapidFilm™ 8mg (treatment a)	Zofran® 8mg Zydis ODT (treatment b)
$AUC_{0-\infty}$ [ng/ml*h]	202.7	214.2
AUC_{0-tz} [ng/ml*h]	193.9	201.3
C_{max} [ng/ml]	28.378	28.650
t_{max} [h]	2.14	2.31

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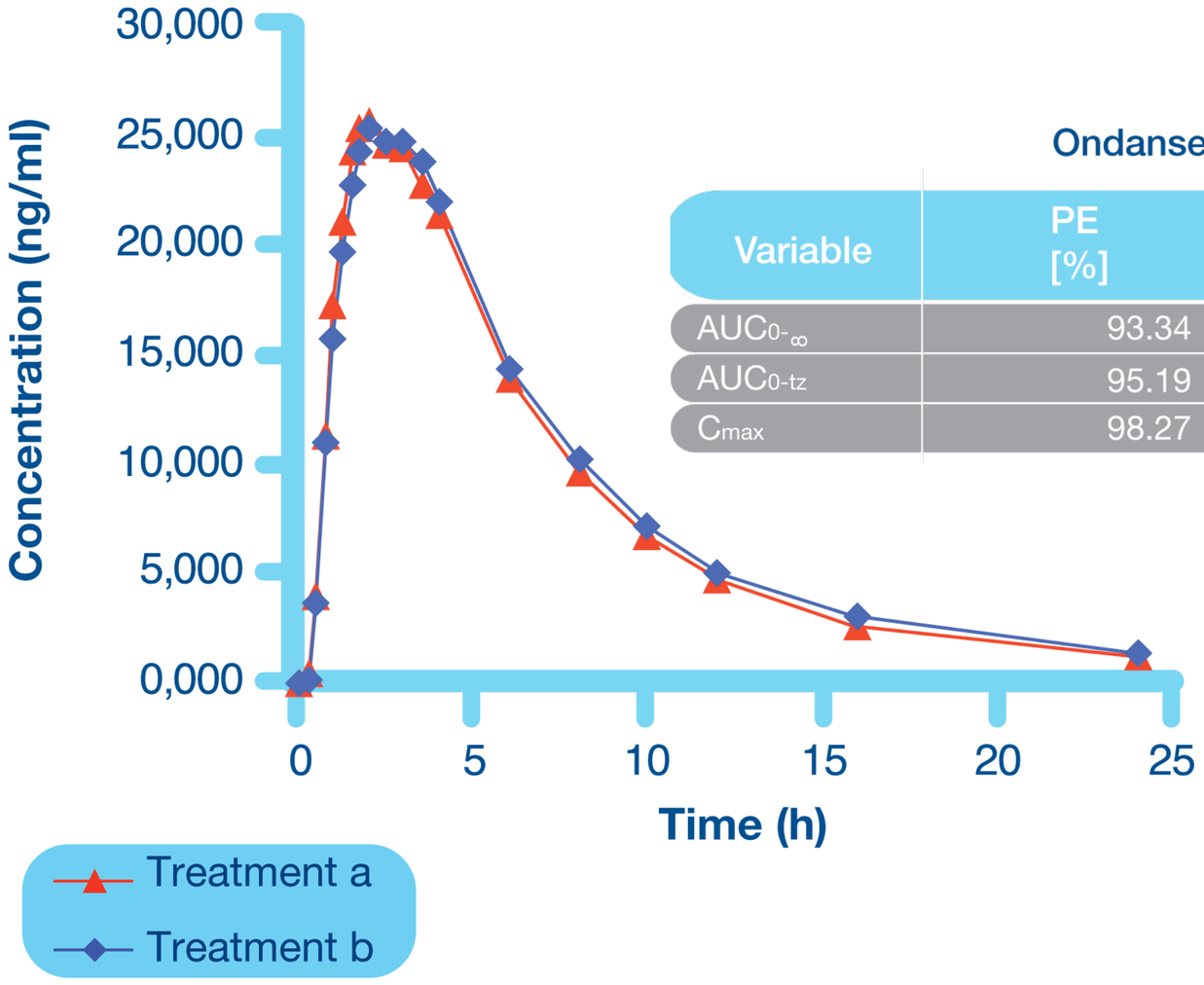


Ondansetron - 90% Confidence Intervals

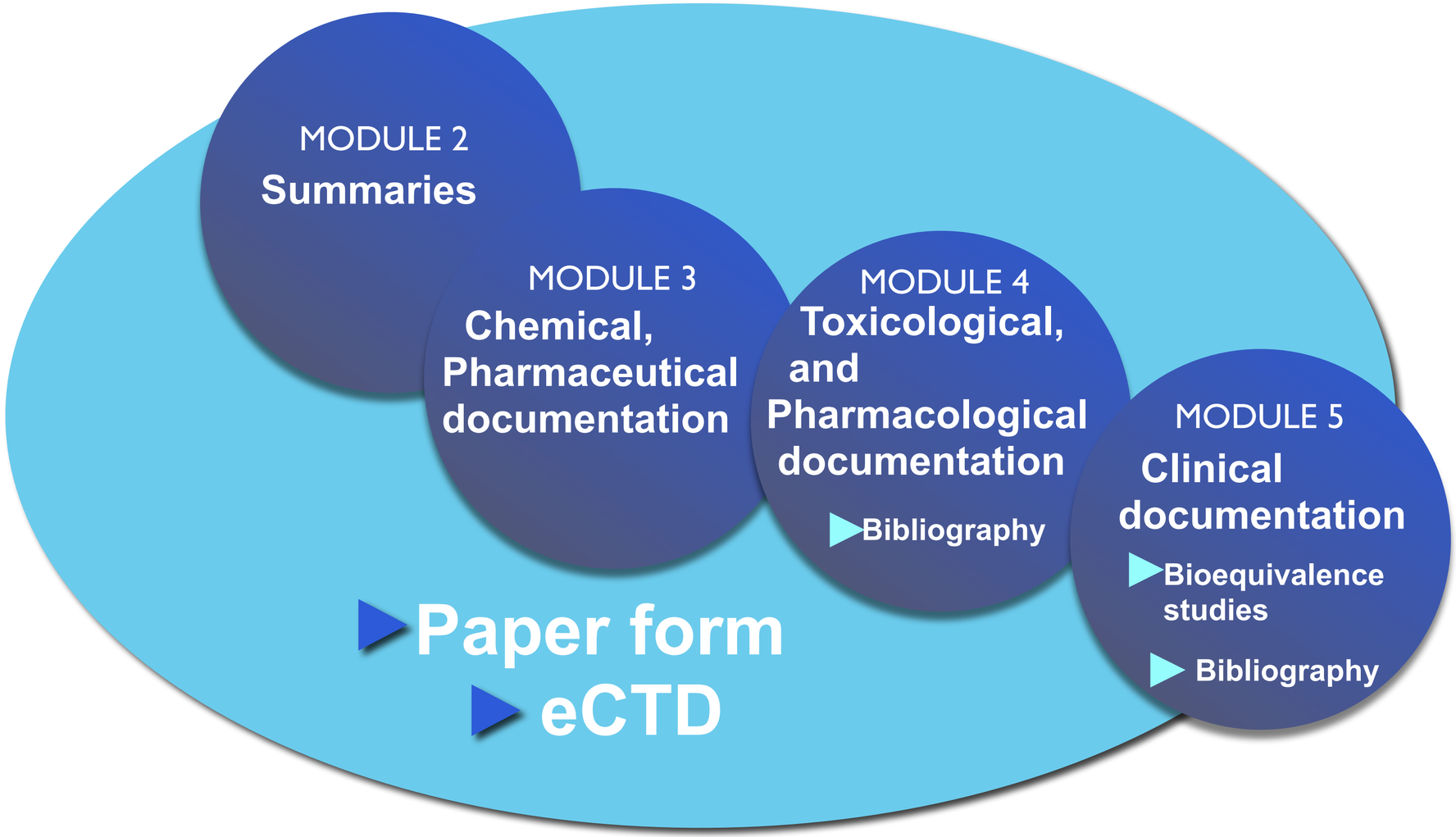
Variable	PE [%]	LL [%]	UL [%]	ANOVA - CV [%]
$AUC_{0-\infty}$	93.34	85.01	102.49	19.0
AUC_{0-tz}	95.19	87.49	103.58	17.2
C_{max}	98.27	91.33	105.74	14.9

a/b are bioequivalent for rate of absorption
Reference interval
[80% , 125%]

a/b are bioequivalent for the extent of absorption
Reference interval
[80% , 125%]

ONDANSETRON DEVELOPMENT

STEP 5: Common Technical Document Preparation



ONDANSETRON DEVELOPMENT

Submission procedure

The finished product was licensed out to companies interested to become the Marketing Authorization Holder and to market **Ondansetron** RapidFilm at national or international level.

EU:license to BioAlliance Pharma SA

The Marketing Authorization Procedure for the dossier of the ondansetron orodispersible film started on 16th February 2009.
The Decentralized Procedure, expected to last 9-12 months, will allow to place the product on the market in 16 EU States.

EXTRA-EU:

Ondansetron RapidFilm has been licensed out for US, the Republic of Korea and Turkey.
Licensing activities in order to secure licensees in the other major worldwide countries are ongoing.

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THANK YOU

FOR YOUR

ATTENTION

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