Biowaiver for MR products
Case study for EU and for ID

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Abbott
A Promise for Life

Introduction

- Abbott
- Established Pharmaceuticals Product Division (EPD):
  - Branded Generics sold over 130 countries
  - Current focus on Emerging Markets
  - ‘Regionalization’
  - Divisional CoP in place

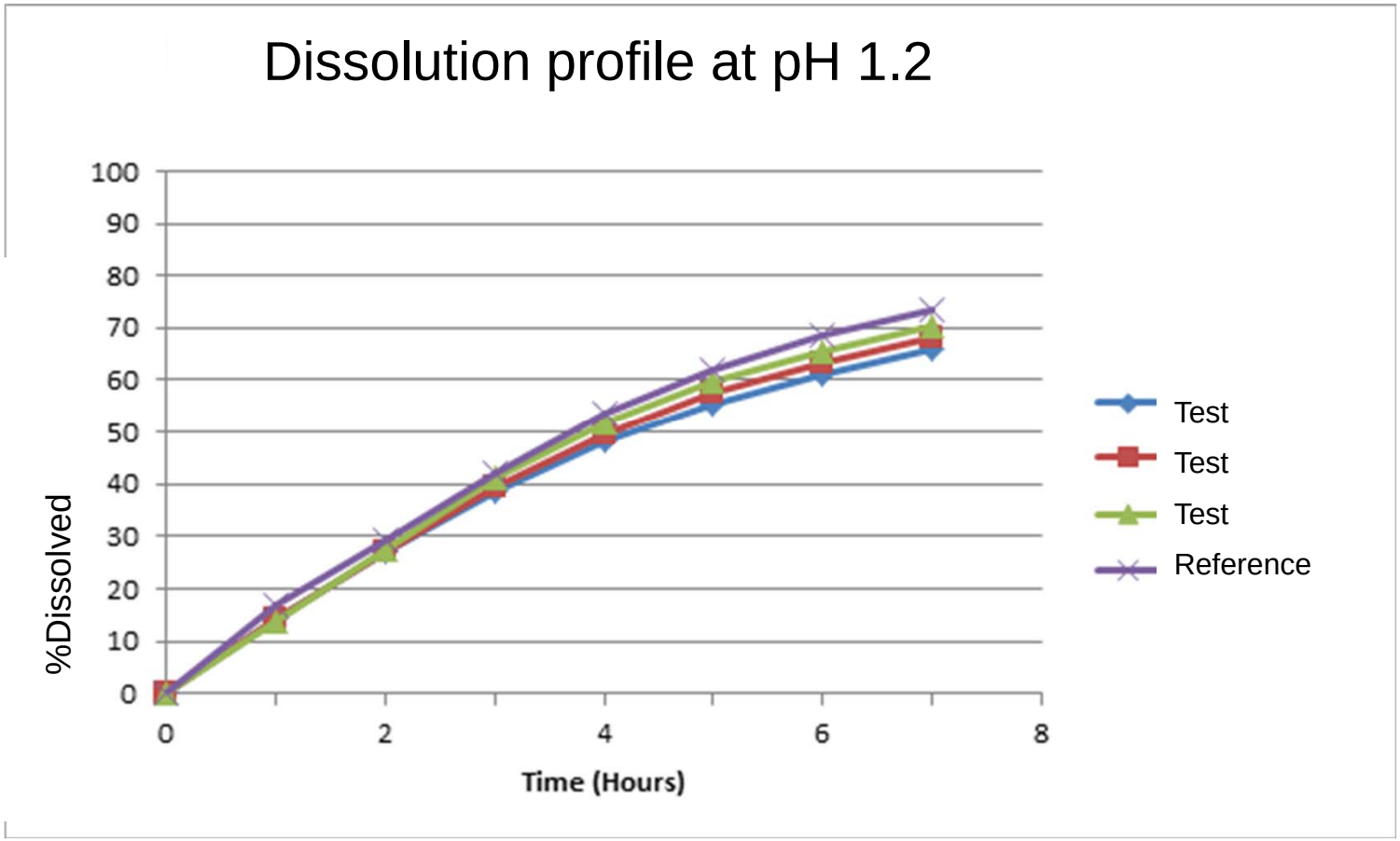
Case study: biowaiver for MR product in EU

- Prolonged release tablet
- Harmonization of formulations (i.e. replacement of formulation)
- No NTI-drug
- Qualitative and quantitative formulations are slightly different
- Grade and source of API other excipients are unchanged
- Manufacturing process and manufacturing site (DE) is the same
- BCS I drug
- Submitted in CH and IT

Composition

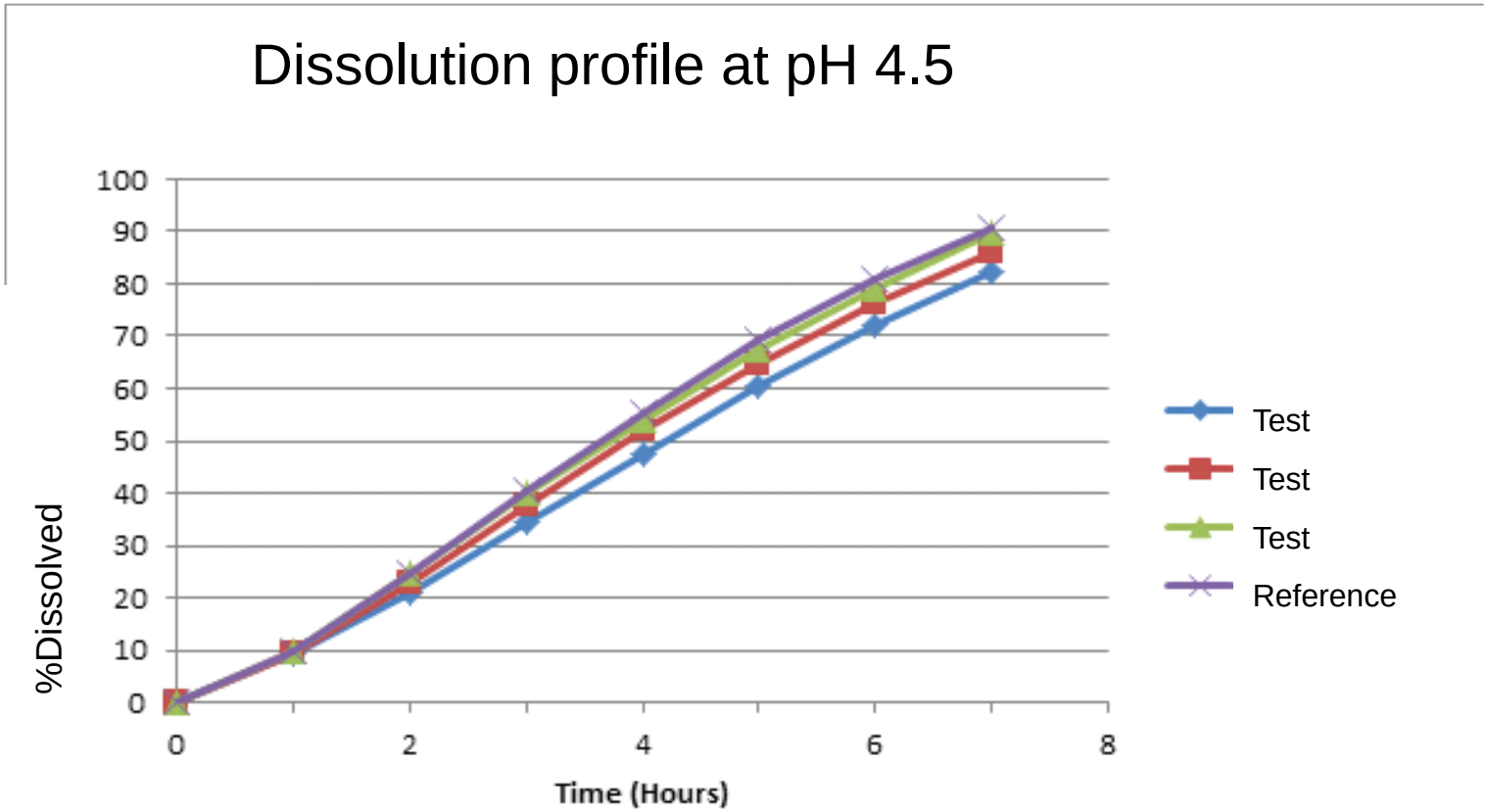
Component	Function	Current	Proposed
Active Substance and Excipients for Tablet Core			
API	Active substance	120.0 mg	120.0 mg
Microcrystalline cellulose	Filler	13.41 mg	39.4 mg
Sodium alginate	Drug release matrix	180.0 mg	160.0 mg
Povidone	Tablet binder	14.11 mg	24.0 mg
Lactose	Filler	8.47 mg	--
Magnesium stearate	Glidant	0.71 mg	1.6 mg
Water, purified	Moisturizer	23.3 mg	15.0 mg
Excipients for Film Coating			
Hypromellose	Coating material	2.823 mg	2.45 mg
Macrogols, type A	Plasticizer	--	0.63 mg
Macrogols, type B	Plasticizer	--	0.42 mg
Macrogols, type C	Plasticizer	0.483 mg	--
Talc	Glidant	4.822 mg	4.20 mg
Titanium dioxide	Coloring agent	3.449 mg	3.15 mg
Sunset yellow	Coloring agent	0.182 mg	--
wax	Polishing agent	--	0.15 mg

Comparative dissolution – pH 1.2



F2= 81, 68 and 80

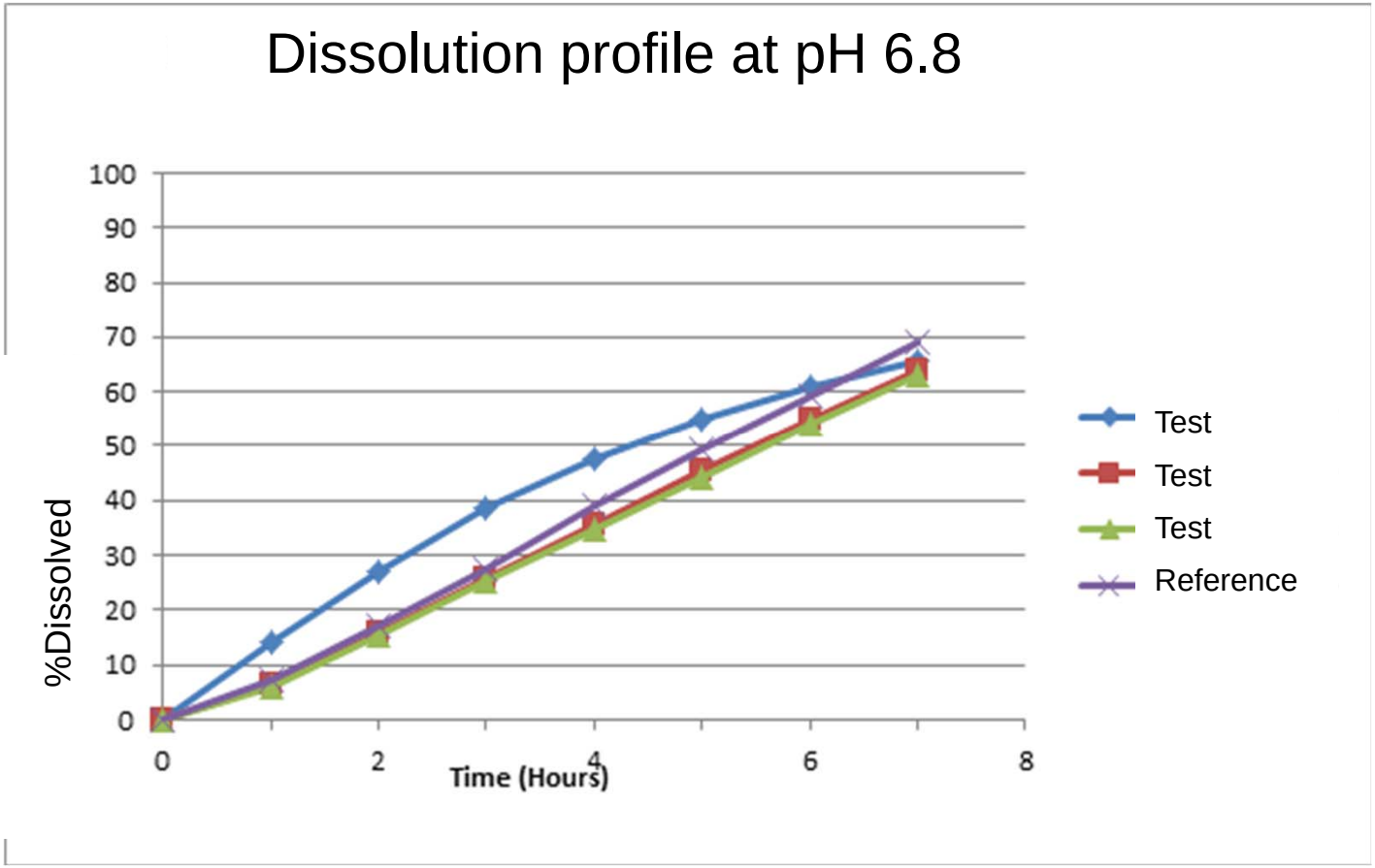
Comparative dissolution – pH 4.5



RSD too high for F2 → multivariate approach (Delta test)* to show equivalence

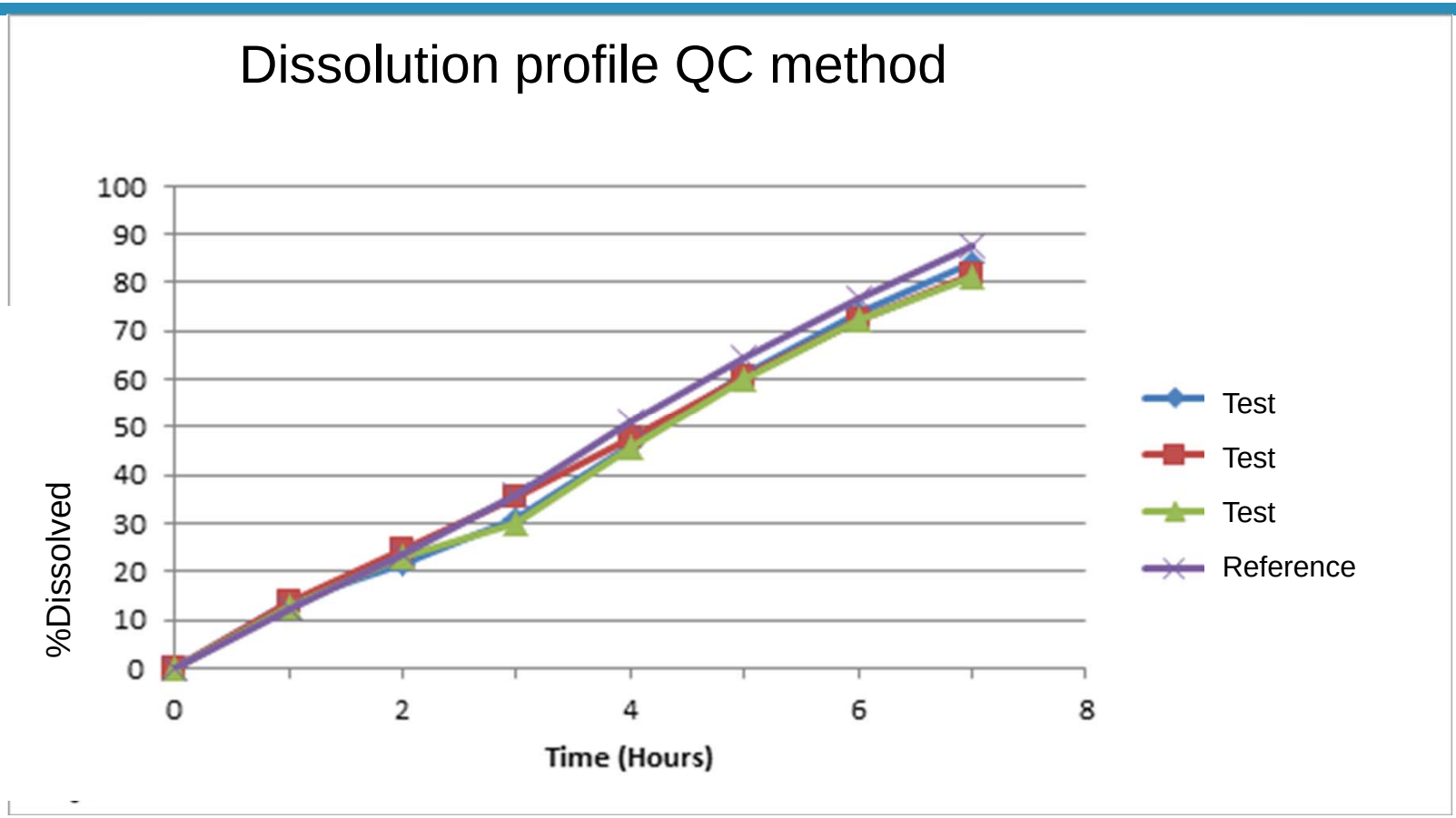
*Saranadasa H and Krishnamoorthy K (2005) A multivariate test for similarity of two dissolution profiles, *J Biopharm Statistics* 15: 265-278.

Comparative dissolution – pH 6.8



F2= 65, 71 and 67

Comparative dissolution – QC release method



RSD too high for F2 → multivariate approach (Delta test)* to show equivalence

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Outcome

- Accepted in IT
- DL received from CH:
  - BCS biowaiver not applicable for MR formulations
  - Answer:
    - Proposed' formulation was previously marketed in CH.
    - Proposed formulation is marketed in several other countries
    - Therefore, no safety concerns

→ Accepted

Emerging markets

- Less harmonization in guidelines (vs EMEA and FDA). KR!
- Communication/Language

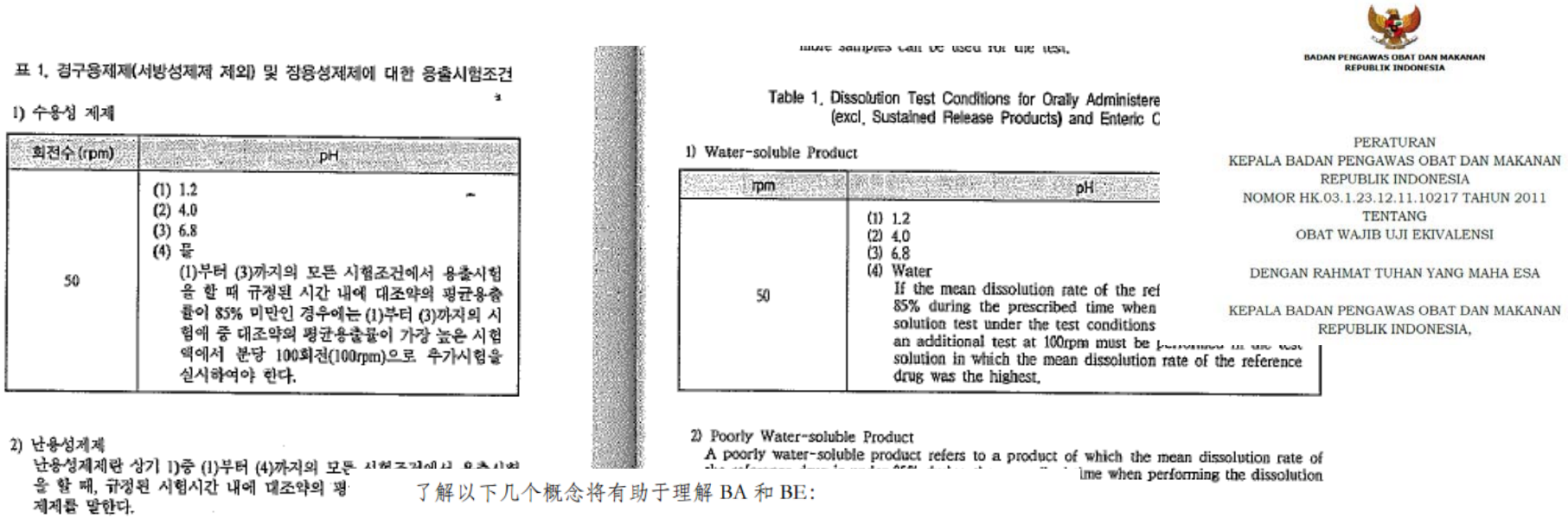

표 1. 경구용제제(서방성제제 제외) 및 장용성제제에 대한 용출시험조건

1) 수용성 제제

회전수 (rpm)	pH
50	(1) 1.2 (2) 4.0 (3) 6.8 (4) 물 (1)부터 (3)까지의 모든 시험조건에서 용출시험을 할 때 규정된 시간 내에 대조약의 평균용출률이 85% 미만인 경우에는 (1)부터 (3)까지의 시험에 중 대조약의 평균용출률이 가장 높은 시험액에서 분당 100회전(100rpm)으로 추가시험을 실시하여야 한다.

2) 난용성제제
난용성제제란 상기 1)중 (1)부터 (4)까지의 모든
을 할 때, 규정된 시험시간 내에 대조약의 평
제제를 말한다.

Table 1. Dissolution Test Conditions for Orally Administere
(excl. Sustained Release Products) and Enteric C

1) Water-soluble Product

rpm	pH
50	(1) 1.2 (2) 4.0 (3) 6.8 (4) Water If the mean dissolution rate of the ref 85% during the prescribed time when solution test under the test conditions an additional test at 100rpm must be solution in which the mean dissolution rate of the reference drug was the highest.

2) Poorly Water-soluble Product
A poorly water-soluble product refers to a product of which the mean dissolution rate of
ime when performing the dissolution

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NOMOR HK.03.1.23.12.11.10217 TAHUN 2011
TENTANG
OBAT WAJIB UJI EKIVALENSI

DENGAN RAHMAT TUHAN YANG MAHA ESA

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA,

了解以下几个概念将有助于理解 BA 和 BE:

原创药（Innovator Product）：是指已经过全面的药学、药理学和毒理学研究以及临床研究数据证实其安全有效性并首次被批准上市的药品。

药学等效性(Pharmaceutical equivalence)：如果两制剂含等量的相同活性成分，具有相同的剂型，符合同样的或可比较的质量标准，则可以认为他

Case Indonesia

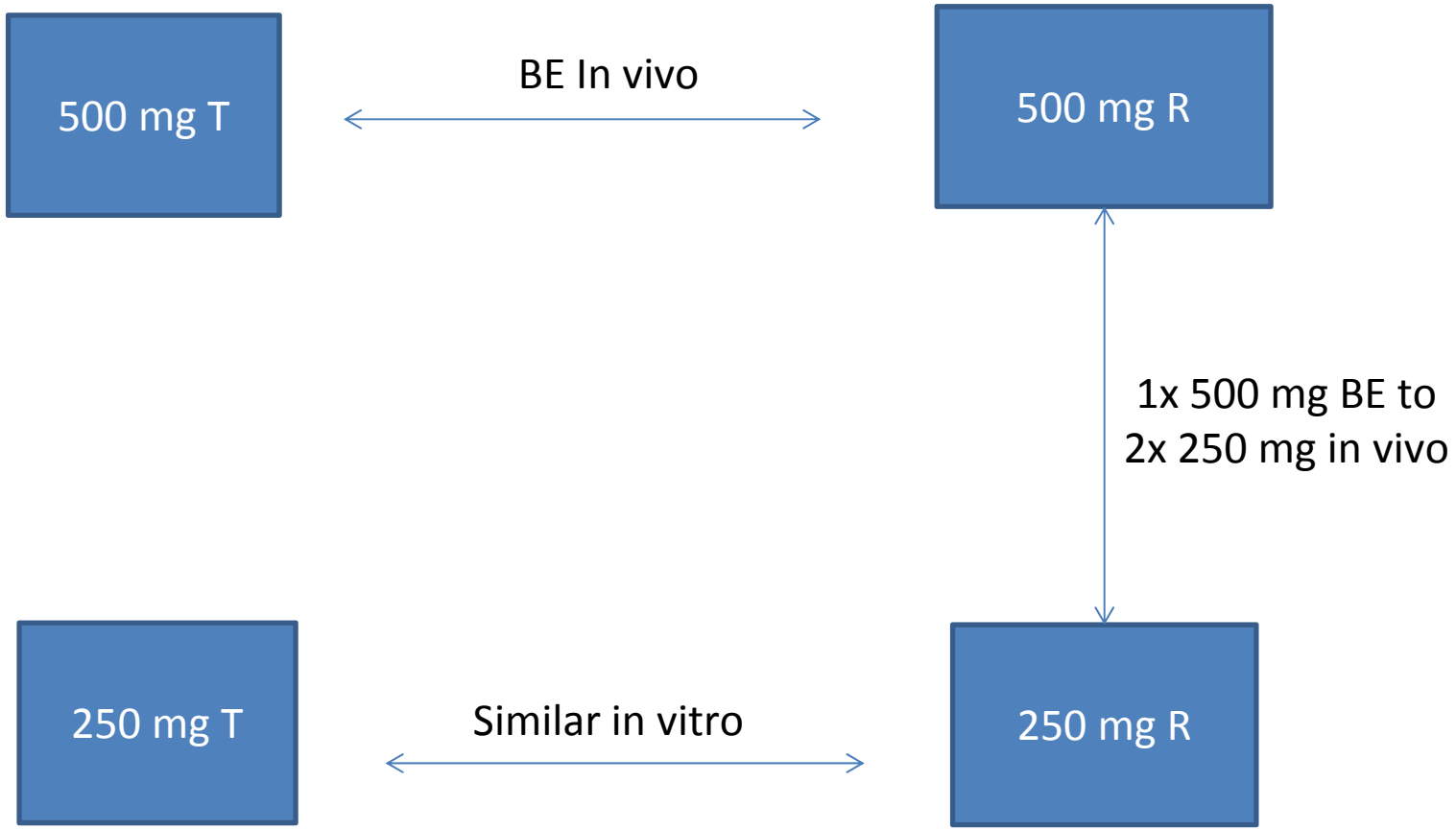
- Situation:
  - Product marketed in Indonesia
  - Site transfer from Puerto Rico to Indonesia

  - Addition of alternative API supplier
  - Extended release formulation
  - Two strengths 250 mg ER and 500 mg ER. For both strengths both variations will apply.

Composition ER formulation

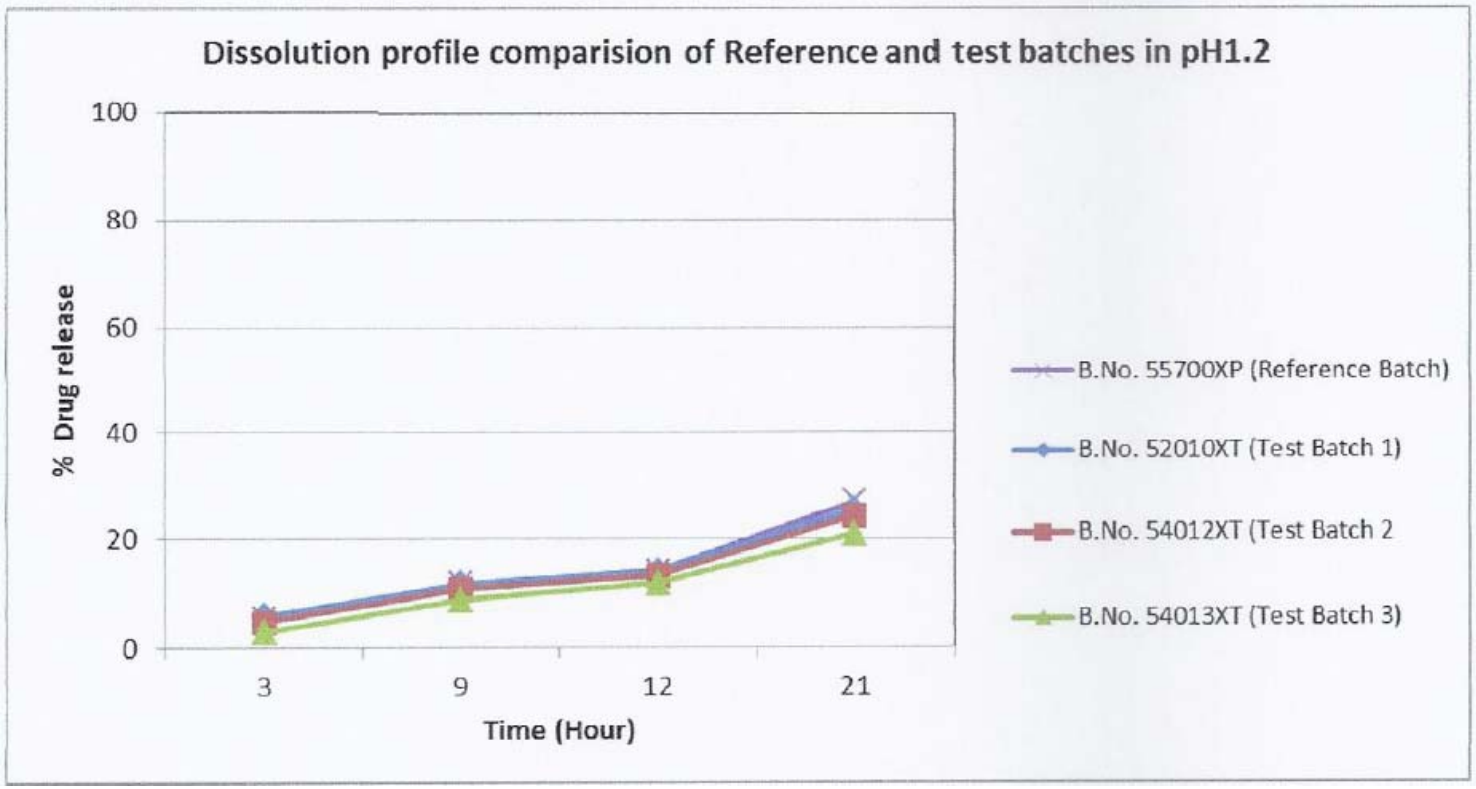
	250 mg ER		500 mg ER	
	Unit Formula		Unit Formula	
Ingredients	mg/tablet	%	mg/tablet	%
API	269.1	41 (% core)	538.1	54 (% core)
Hypromellose (rate controlling polymer)	292.5	45 (% core)	300	30 (% core)
Cellulose Microcrystalline	62.4	10 (% core)	50	5 (% core)
Lactose monohydrate			81.9	8 (% core)
Silicon Dioxide	26	4 (% core)	30	3 (% core)
Total (tablet core)	**650**	**100**	**1000**	**100**
Color coating (non-functional)				
Potassium Sorbate	0.13	0.02 (%tablet)	0.2	0.02 (%tablet)
Opadry II	26	3.79 (%tablet)	40	3.81 (%tablet)
Clear coating (non-functional)				
Potassium Sorbate	0		0.2	0.02 (%tablet)
Opadry	9.75	1.42 (%tablet)	10	0.95 (%tablet)
Total (core + coating)	685.88		1050.2	

Strategy



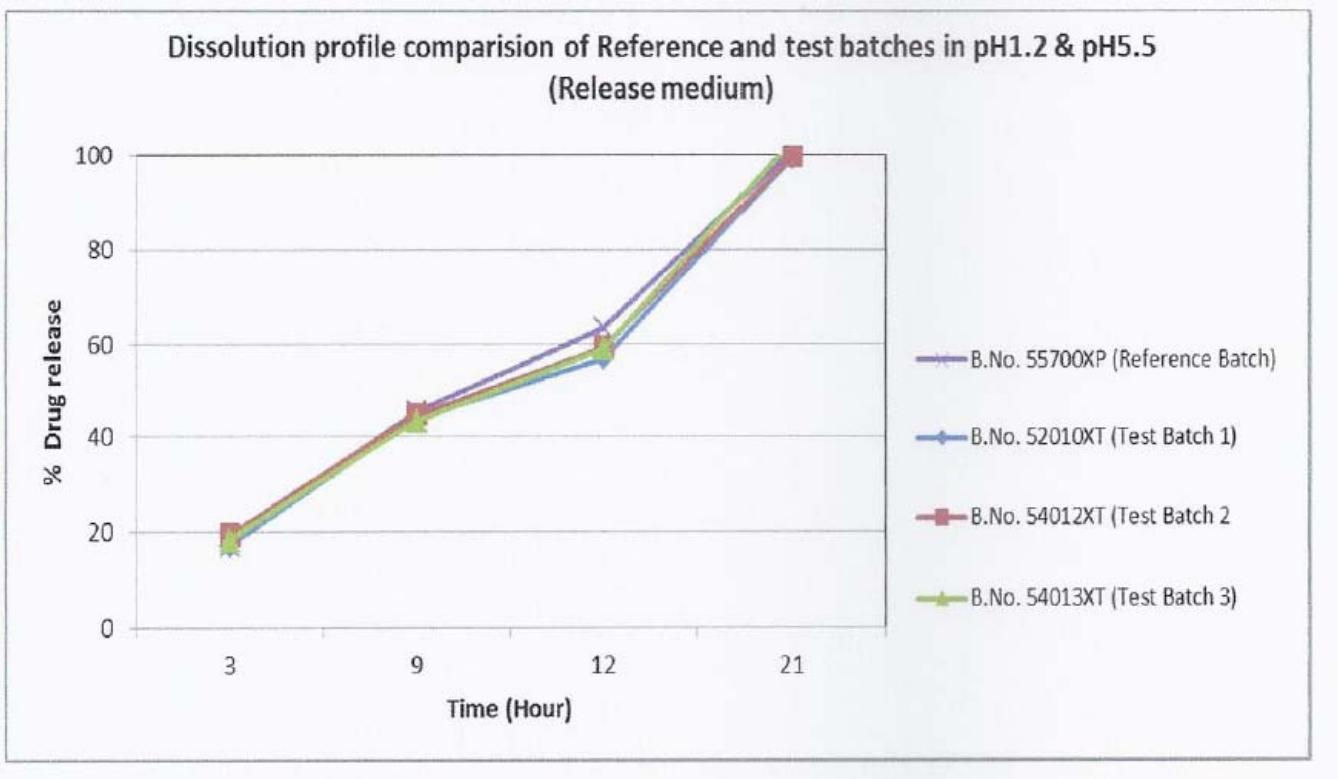
Comparative dissolution – 250 mg ER

- pH 1.2. F2: 95, 92, and 94



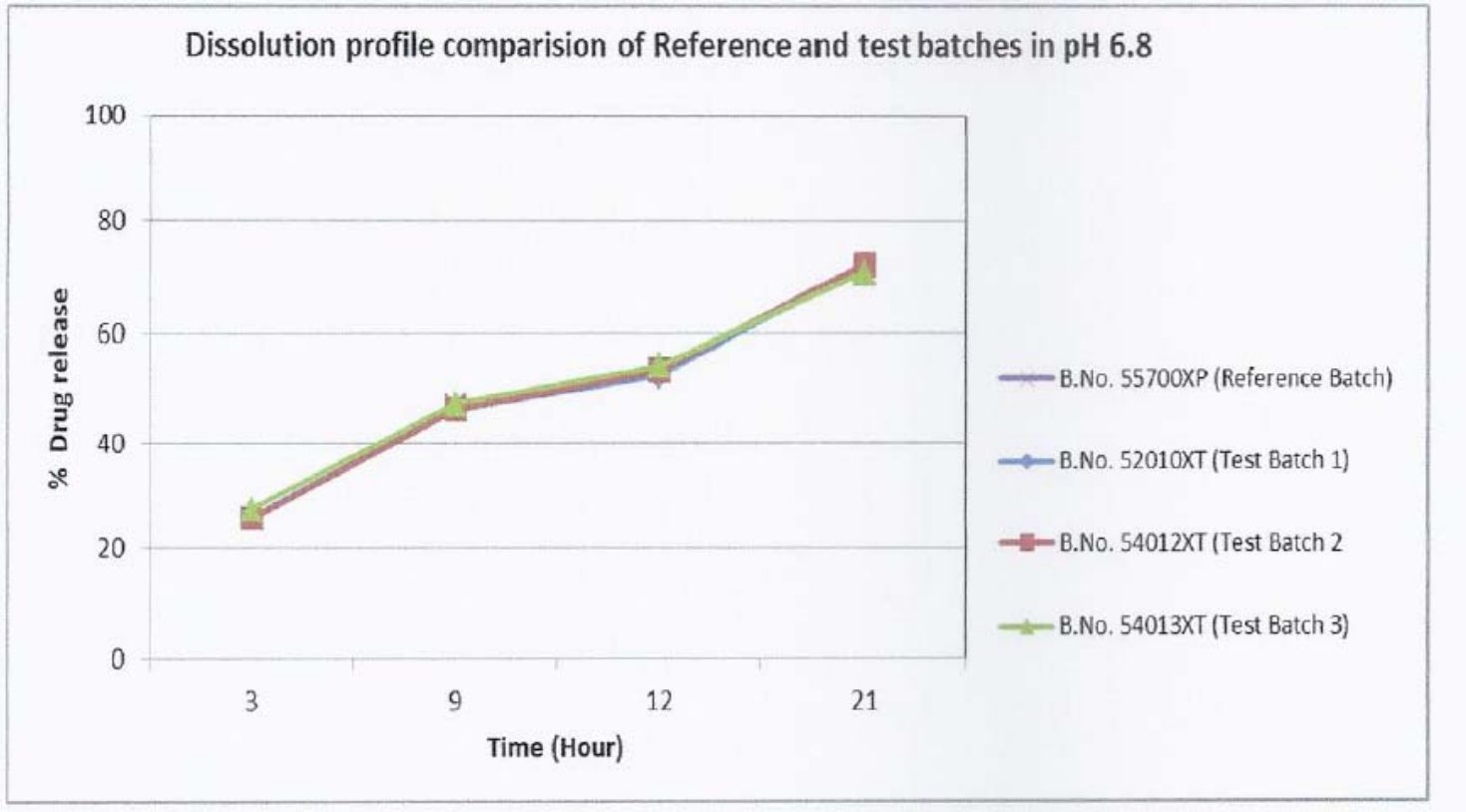
Comparative dissolution – 250 mg ER

- pH 1.2 (45 min) followed by pH 5.5 (= QC release method)
- F2: 81, 82, and 81

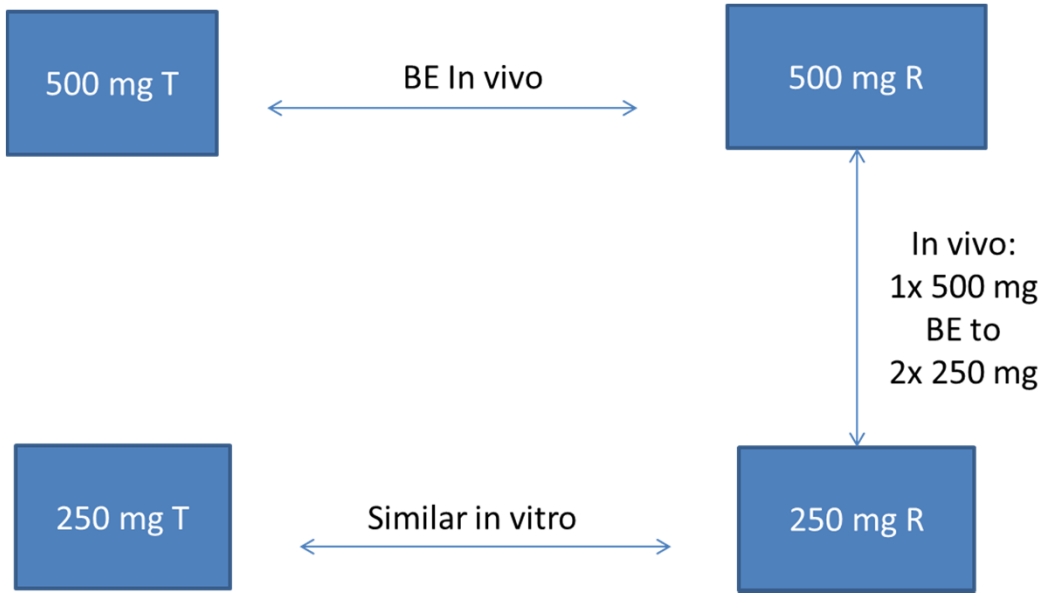


Comparative dissolution – 250 mg ER

- pH 6.8. F2: 92, 94, and 95



Discussion

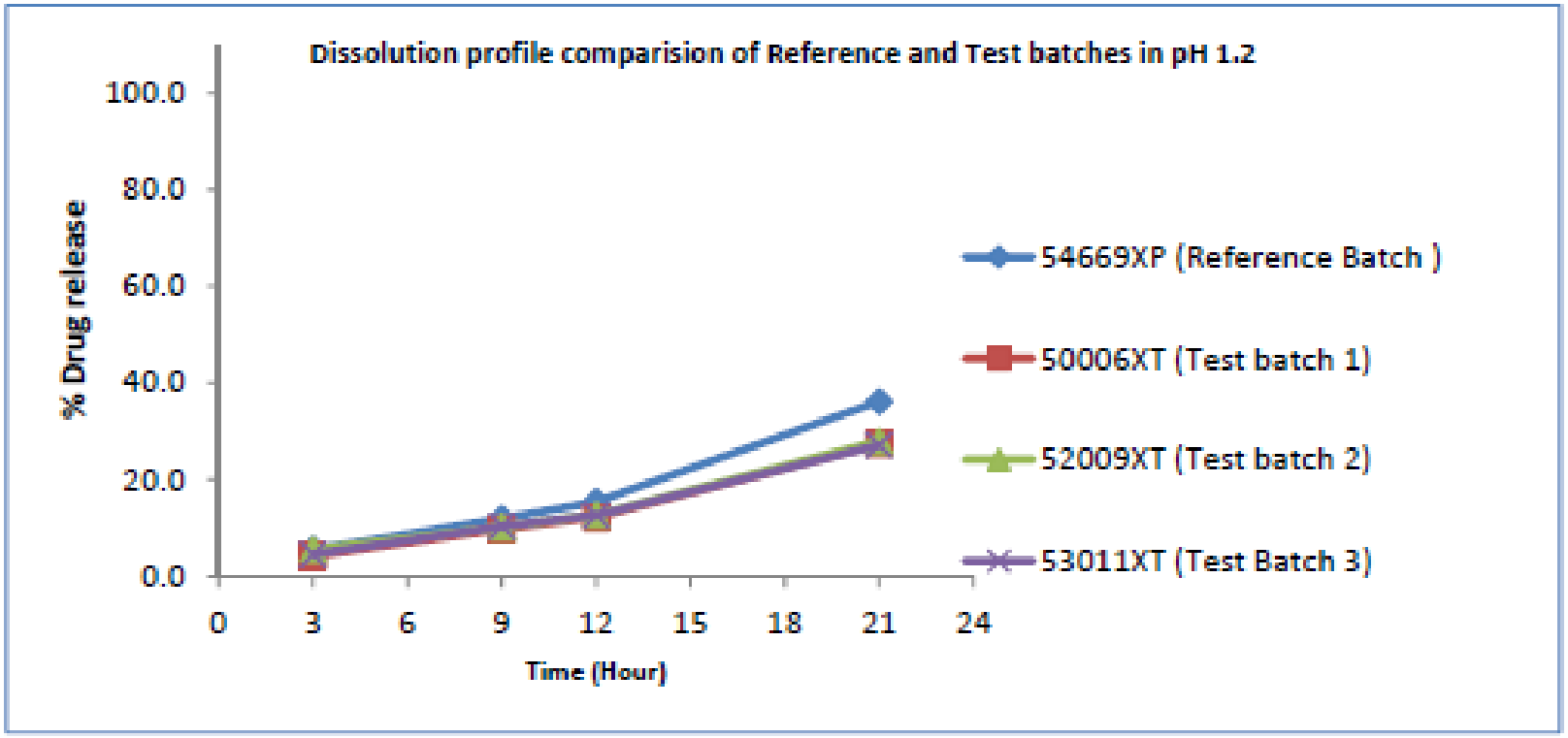


- Would this approach work in EU?
- What about RoW?

Back-up slides

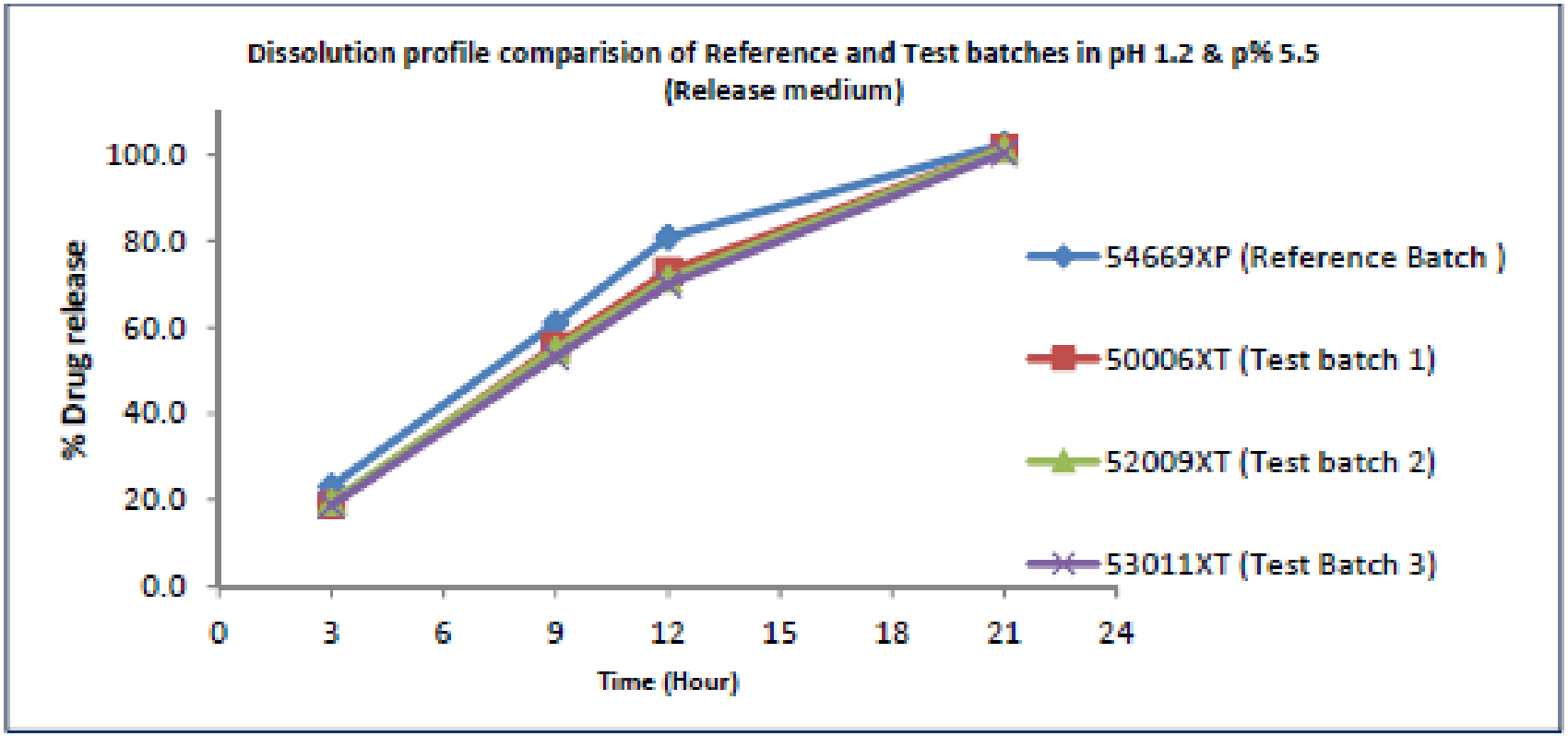
Comparative dissolution 500 mg ER (for case ID)

- pH 1.2 (F2: 77 – 79)



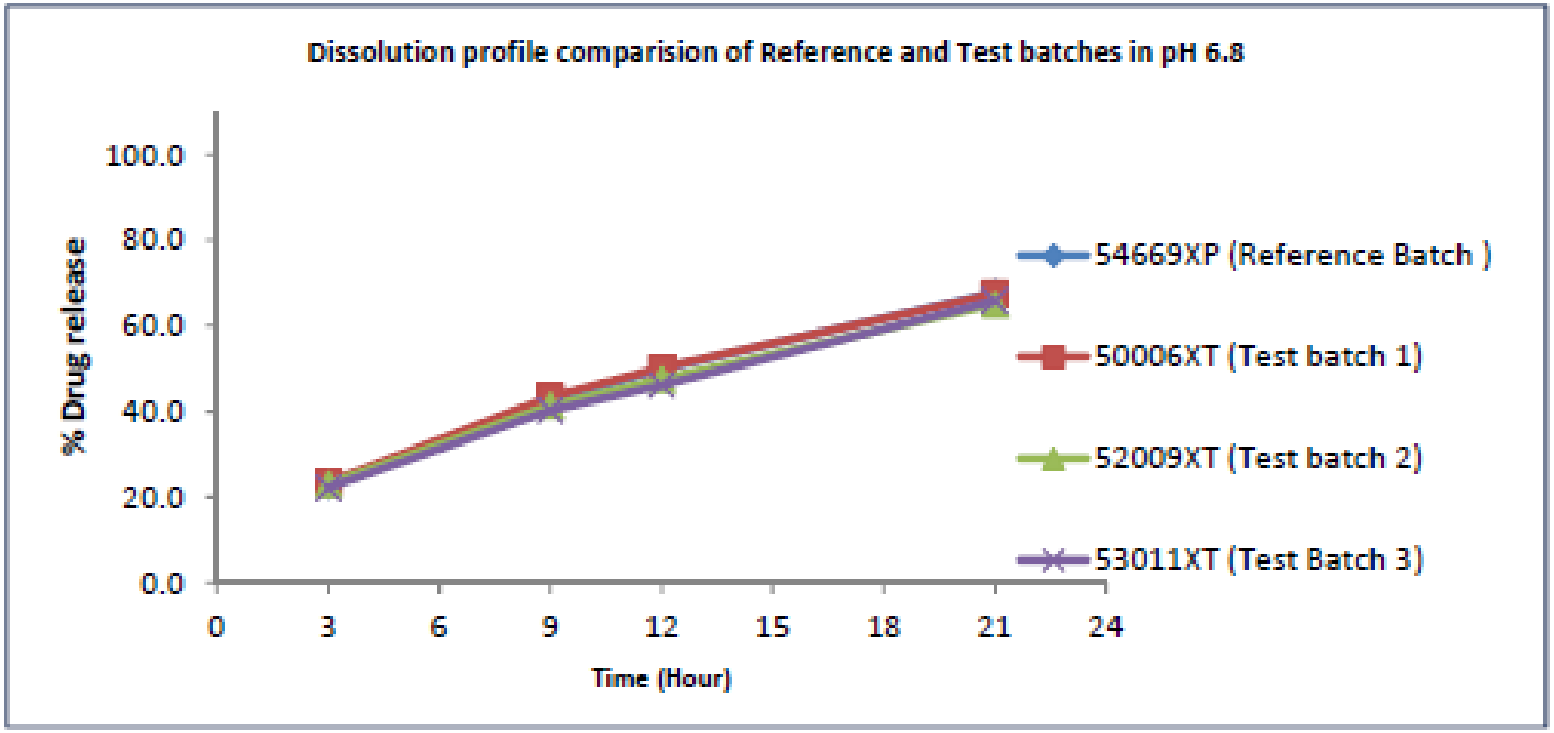
Comparative dissolution 500 mg ER (for case ID)

- pH 1.2 followed by pH 5.5 (= QC release method). F2: 70-72



Comparative dissolution 500 mg ER (for case ID)

- pH 6.8. F2: 87 - 89



South Korea comp disso - 1

- KR is quite specific about conditions for comparative dissolution
- Different conditions for water soluble products, poorly soluble products, enteric coated (EC), EC with poorly soluble drugs, extended release products
- Example enteric coated product: pH 1.2, pH 6.0, pH 6.8

3) Enteric-coated products

Agitation(rpm)	pH
50	(1) 1.2 (2) 6.0 (3) 6.8

When dissolution test is performed under the test condition (2), and the average dissolution of reference drug does not reach 85% within the testing time point specified, an additional test in solution (2) with an agitation by 100 rpm shall be performed.

South Korea comp disso - 2

- Acceptance criteria for equivalence of profiles (DR)

b. When dissolution of the reference drug has a lag time

1) When the average dissolution of the reference drug reaches 85% within 15 min after the lag time: Judged as equivalent if the difference in lag time between the two products is less than 10 min and the average dissolution of the test drug reaches 85% within 15 min after the lag time or the average dissolution of the test drug is within that of the reference drug ± 15 % at around 85%.

2) When the average dissolution of the reference drug reaches 85% at between 15 and 30 min after the lag time: Judged as equivalent if the difference in lag time between the two products is less than 10 min and the average dissolution of the test drug are within that of the reference drug ± 15 % at two appropriate time points when the average dissolution of the reference drug are around 60% and 85%, or the similarity factor(f_2) is not less than 50.

3) Others: Judged as equivalent if the average dissolution of the test drug are within that of the reference drug ± 15 % at two appropriate time points when the average dissolution of the reference drug are around 40% and 85%, or the similarity factor(f2) is not less than 50.

○ Lag time: When dissolution is delayed, it is defined as the time when 5 % of the active pharmaceutical ingredient dissolves and determined by linear interpolation at two appropriate time points when the average dissolution of the reference and test drug are around 5%.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