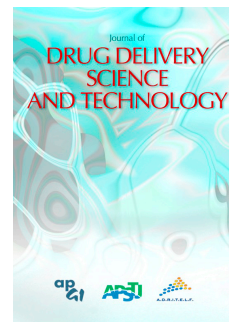


Journal Pre-proof

Approaches to supply bioequivalent oral solid pharmaceutical formulations through the lifecycles of products: Four-media dissolution monitoring program in Japan

Ken-ichi Izutsu, Yasuhiro Abe, Hiroyuki Yoshida



PII: S1773-2247(19)31221-3

DOI: <https://doi.org/10.1016/j.jddst.2019.101378>

Reference: JDDST 101378

To appear in: *Journal of Drug Delivery Science and Technology*

Received Date: 18 August 2019

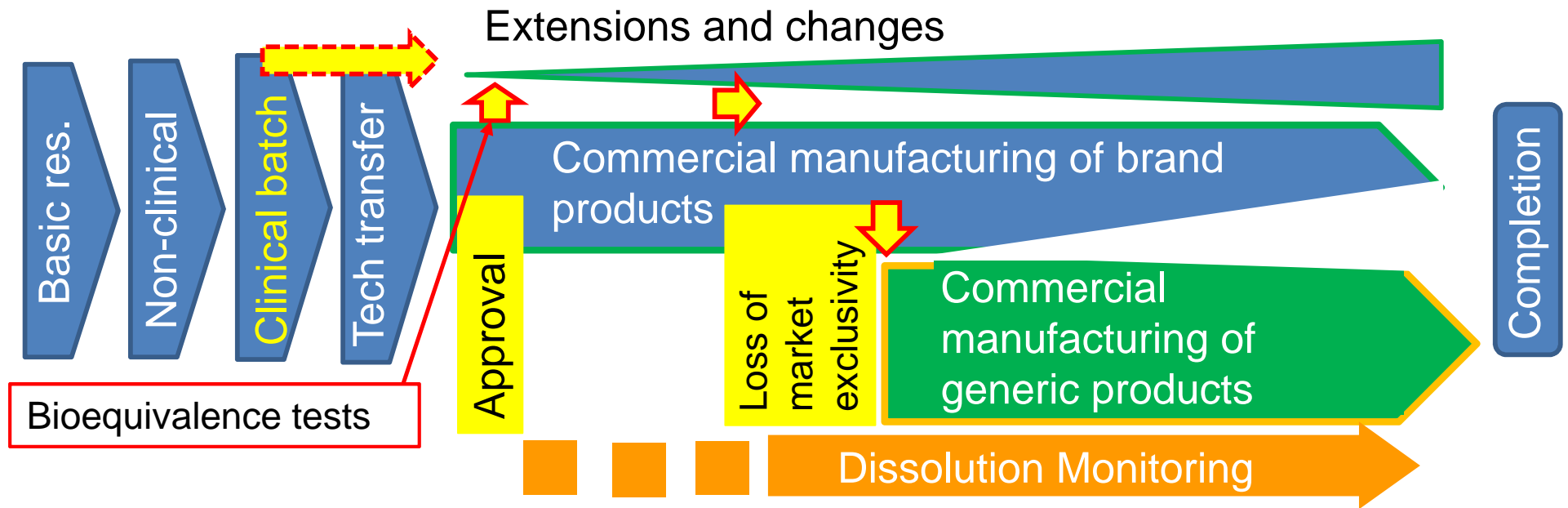
Revised Date: 8 November 2019

Accepted Date: 8 November 2019

Please cite this article as: K.-i. Izutsu, Y. Abe, H. Yoshida, Approaches to supply bioequivalent oral solid pharmaceutical formulations through the lifecycles of products: Four-media dissolution monitoring program in Japan, *Journal of Drug Delivery Science and Technology* (2019), doi: <https://doi.org/10.1016/j.jddst.2019.101378>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier B.V.



Approaches to supply bioequivalent oral solid pharmaceutical formulations through the lifecycles of products: four-media dissolution monitoring program in Japan

Ken-ichi Izutsu*, Yasuhiro Abe, Hiroyuki Yoshida

Division of Drugs, National Institute of Health Sciences

3-25-26 Tonomachi, Kawasaki-ku, Kawasaki, Kanagawa 210-9501, Japan

*Corresponding author: izutsu@nihs.go.jp

Abstract

The continuous supply of pharmaceutical formulations therapeutically equivalent to the clinical batches used during development is important to ensure their safety and efficacy. The development of new generic drugs and the postapproval changes of the formulations (e.g., dosage form, dose strength, and composition) and manufacturing (e.g., facility and ingredient) require bioequivalence tests following the appropriate guidelines. Maintaining the formulation performance in the commercial production phase is often more challenging due to multiple manufacturing and stability factors affecting dissolution. A case of a product out of the bioequivalence range between batches in a post-marketed human study emphasized the risk. This minireview introduces multiple approaches to prevent significant bioinequivalence between batches and products through their lifecycles, focusing on a periodical dissolution-monitoring program using four media (acidic, intermediate, neutral, and water) in Japan. Setting the same procedure to monitor one of the complex critical quality attributes should

efficiently reduce patient risk complementarily with appropriate specifications and GMP manufacturing.

Keywords

Dissolution; Product lifecycle; Bioequivalence; Monitoring; Tablet; Generic

1. Introduction

Supplying therapeutically equivalent formulations throughout the lifecycle is necessary to ensure their efficacy and safety as evaluated in clinical trial batches of brand products. Significant changes in the bioavailability would expose patients to safety risks, particularly in altering the batches and/or products (e.g., innovator–generic and generic–generic). The increasing number of lower-solubility biopharmaceutical classification (BCS) 2 and 4 active pharmaceutical ingredients (APIs) emphasizes the importance of controlling their dissolution in oral solid dosage forms. Bioequivalence tests applied in the development of new formulations and their postapproval changes play a pivotal role in maintaining the bioequivalence between products, as shown in a schematic figure of their lifecycles (Fig. 1).

Changes in product performance during the long commercial production phase pose another challenge in maintaining the bioequivalence between batches and products and ensuring their exchangeability. Various factors, including the physical state of the APIs (e.g., crystal form, hydrate/solvate, crystallinity, residual water, and particle size), excipients (e.g., MW and particle size), processes (e.g., granulation methods, mixing

state, and tableting force), and testing conditions (e.g., device vibration, vessel structure, sampling probe positions, deaeration methods, and filter types) may unintentionally affect the dissolution of solid formulations in the production batches (1). This short review introduces several measures to maintain the bioequivalence of oral solid dosage forms, focusing on a performance-monitoring program using a four-media dissolution test in Japan. The contributions of formulation design, specifications, and GMP manufacturing to support robust product performance are also discussed.

2. Bioequivalence guidelines on changes and extensions

Bioequivalence tests using healthy volunteers and/or other surrogate *in vitro* methods (e.g., dissolution) are performed during the development phase (e.g., formulation extensions and development of new generic formulations) and postapproval changes of the formulation (e.g., excipient composition) or manufacturing (e.g., site change) to ensure the product's effectiveness and safety as studied in the pivotal batch. Organized bioequivalence study guidelines categorize the required tests depending on the risk of a change in the formulation's performance (1–6). *In vitro* characterization of the APIs and formulations provides an opportunity to waive the need for human bioavailability study (e.g., BCS-based biowaiver) (7). The U.S. Food and Drug Administration and the European Medicines Agency provided some product-specific guidelines for the development of new generic formulations (8, 9). Effective pharmaceutical quality system (PQS) and change management discussed in ICH Q12 should further assist the risk-based approach (10).

3. Bioequivalence in the production phase

Maintaining the formulation performance during the commercial production phase, in the absence of postapproval changes, is another important issue to maintain therapeutic equivalence throughout the product lifecycle. Variation in the physical state of formulation components and process variables would alter the dissolution and resulting bioavailability of oral solid formulations. The accumulation of moderate differences in performance at the postapproval changes during the lifecycle can also induce bioinequivalence relative to the initial formulation.

A case of batches out of the bioequivalence range of a brand itraconazole capsule formulation in 2008 emphasized the importance of controlling product performance during the commercial production phase in Japan (11). This issue was raised after multiple generic pharmaceutical manufacturers reported large variations and/or changes in the dissolution of the brand product. Later batches of the particular product showed much faster dissolution, with all of them meeting the specifications. The difference in dissolution profiles between batches of the product was more apparent in the test using certain media (e.g., lower polysorbate concentrations: 1%). Thus, the Ministry of Health, Labor and Welfare (MHLW) and its Expert Committee on Quality of Generic Drug Products (ECQGDP) asked the innovator company to run a human bioequivalence study between the old and newer batches of the product. This human study resulted in the finding of bioavailability study data (C_{max} and AUC_{48}) out of the bioequivalence criteria in the respective guidelines. Assessment of the formulation and manufacturing process suggested the contribution of some process-related changes (e.g., variation in the coating) as possible causes of the increased dissolution.

4. Formulation design and GMP manufacturing

The combination of the appropriate design, its implementation, and monitoring should be a desirable approach to supply bioequivalent formulations throughout product lifecycles. Rational formulation and process design by the QbD approach is a powerful tool to achieve robust product performance (12–14). GMP manufacturing based on a rational control strategy contributes to reducing unintended changes due to the altered character of components and/or unit operations (e.g., granulation, mixing, and tableting), which affect bioavailability in the commercial production phase (15). Process analytical technologies (PAT) should assist in the appropriate process control. It is, however, not realistic to control all of the possible factors in the manufacturing process (16, 17).

5. Specifications

Dissolution specifications, in combination with the respective test methods, are the main and direct measures to support batch-to-batch consistency of the performance of products throughout their lifecycles. Many IR dosage forms have single-point dissolution specifications that stipulate a lower acceptable dissolution rate under the specific test conditions, including the apparatus (e.g., paddle and basket), media (e.g., compendial buffers in acidic to neutral pH), string speed (e.g., 50 rpm), sampling time, and temperature ($37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$). The dissolution test method and the specifications of each formulation are usually set based on the performance of the formulations used in the biobatch (e.g., pharmacokinetic evaluation or bioequivalence test batches), enabling simple batch release tests. The MHLW conducted annual surveys of ethical pharmaceutical products distributed in Japan in official medicine control laboratories, which found seven products out of the dissolution specifications among 2651

formulations in 5 years (fiscal years 2013–2017).

Despite the major contribution of the specifications to preventing batches with lower dissolution, they should have some limitations in maintaining the performance of products through their lifecycles. Single-point specifications defining the lower limit of dissolution allow much faster dissolution, which may lead to faster absorption and higher C_{max} . The relevance of the test conditions (e.g., pH) and criteria of the dissolution specification should be another issue. The specification test can also overlook the change in dissolution in solutions of other pHs. Ideally, the test should find the bioequivalent formulations based on sufficient pharmacokinetic data (18–20). Some new approaches in setting the specifications use the bioequivalence border obtained through *in vitro* and *in vivo* data, as well as biopharmaceutical modeling (21–24). However, many dissolution specifications are not sufficiently related to the *in vivo* performance of the formulations due largely to the limited *in vivo* data. Some dissolution specifications can distinguish only significantly slower batches manufactured with apparently different process parameters and/or critical quality attributes (CQA; e.g., size of API crystal) (18). Some tests using certain higher-dissolution-rate media (e.g., acidic solutions and high-concentration surfactant solutions) have insufficient discriminatory powers to find the changes in formulation performance. For many generic products, there is no *in vivo* performance information for the particular formulation. Thus, additional measures to monitor and control the formulation performance should have a reasonable chance of mitigating the risk of bioequivalence between batches in the commercial production phase.

6. Monitoring of formulation performance by four-media dissolution studies

The MHLW and ECQGD introduced a nonbinding measure to monitor similarity in dissolution profiles of the reference brand product and generic products in 2007 as part of a multidisciplinary program to promote the use of generic drugs based on patient acceptance (Action Program for the Promotion of the Safe Use of Generic Drugs) (11). This approach is aimed at mitigating the risk of significant bioinequivalence in the long product lifecycles, avoiding extremely strict specifications. Improving the perception of healthcare professionals and patients regarding the quality of generic drugs is necessary to achieve the government policy of rapidly increasing the use of ethical generic drugs in a decade (from a share of approximately 30% to 80%) to ease the growing burden of national health insurance costs. Cooperation with the industry contributed to the implementation of a nonbinding approach.

In the manufactures of generic products, it is recommended to periodically run dissolution tests in four media representing physiological pH ranges in different parts of the gut tract (pH 1.2, 3.0–5.0, and 6.8) and water. Water is included as a simple medium with low-buffer-capacity and high power for discriminating different dissolution properties between products. The dissolution profiles are compared with those of (1) the current brand product or (2) the bioequivalence study batch (biobatch) of the particular generic product as references. Products showing dissolution out of the similarity range of both of these profiles are subjected to the adjustment of the performance by appropriate measures (e.g., altering the tablet compression force) within a certain period. The dissolution similarity of the reference and generic formulations is assessed by the similarity factor (f_2) and dissolution difference at certain timepoints (Table 1) (25).

The dissolution profile of the product obtained at the time of development (biobatch) is included as a reference because (1) the property of some current brand products changes from the pivotal batch and (2) some generic products originally have different dissolution profiles from that of the brand formulation at the time of their development with a human bioequivalence study. The scheme emphasizing similarity in dissolution profiles between formulations in multiple media was originally derived from postapproval change guidelines for IR solid oral dosage forms (1, 26).

For products that are listed in the Quality Re-evaluation of Ethical Drug (QRED) program, the dissolution profiles of both (1) the current brand product and (2) those listed in the Japanese Orange Book are used as references for the respective generic products. The QRED program was run from 1997 to 2012 to avoid significant bioequivalence between the reference innovator products without appropriate dissolution specifications at the time and their generic formulations (638 APIs and 4588 products approved with a human bioequivalence study in old guidelines) by coordinating the dissolution profiles in four media. Standard dissolution profiles of the brand products obtained by official laboratories were listed in the program reports (Japanese Orange Book).

The Working Group of the ECQGD, consisting of the NIHS, NIID, and prefectural health institute laboratories, runs four-media dissolution measurements to obtain the profiles of 100 to 150 products per year. The group obtained dissolution profiles of the test and corresponding reference products up to 360 min or until the profile reached a plateau. The similarity of the dissolution profiles obtained usually at 15, 30, and 45 min

is evaluated from the difference in the dissolution rate and using f_2 values. Slightly wider acceptable ranges of the parameters than those in the bioequivalence test guidelines are applied for comparison of the dissolution profiles (Table 1). Dissolution profiles of 67 products (approximately 5.3%) were out of the similarity range relative to the reference profiles in at least one of the media in 1261 formulations evaluated in a decade (between FY 2008 to 2017). The ECQGD recommends checking the formulation properties and the manufacturing process of the products out of the similarity range of at least one of the media. Some manufacturers found changes in the API particle size and coating thickness as the causes of the change in the performance of the batch. Improvement of a formulation requires various amounts of time depending on the causes and measures required to remedy the problem. Examples of the four-media dissolution profiles are shown in Fig. 2 (spironolactone tablets, 25 mg) and Fig. 3 (glimepiride orodispersible tablets, 1 mg). All of these formulations met the specifications of spironolactone (water, 45 min, 70%) and glimepiride (pH 7.5, 15 min, 75%) products. Similar dissolution profiles between products were observed in many formulations, while some showed varied profiles in certain media. Fig. 4 shows the dissolution profiles of atenolol tablet formulations (50 mg) obtained in 2012 and 2014. The dissolution profile of one of the generic products was out of the similarity range relative to the brand product (current, Orange Book). The performance of the generic product was adjusted after the monitoring report. The Committee provides precise data, including the dissolution profiles and other quality items (e.g., purity of injectable formulations), with some explanations and manufacturer's comments on its webpage (27).

7. Discussion

The bioequivalence of oral dosage formulations in the commercial production phase has not been sufficiently dealt with in the regulation despite the potential clinical risks. The four-media dissolution monitoring works as a relatively simple method to reduce the risk of significant bioinequivalence through the lifecycles. Combinations of the appropriate design, manufacturing, and monitoring should contribute to the supply of bioequivalent formulations in the short- and long-term. Confirmation of the dissolution specification in shipping tests and periodical monitoring of the profiles should complementarily contribute to preventing large unidentified changes in the product performance. Applying the same procedure to all generic oral solid formulations would also ensure exchangeability with less risk of bioinequivalence between them. The assessment may also be regarded as a method to monitor and maintain the state of control of the product quality (e.g., CQA) and performance during commercial production, as described in the ICH pharmaceutical quality system guidelines (Q10). Modification of the method, including the use of media closer to physiological gut fluid (e.g., low-buffer-capacity solution), would be an option to improve the relevance of monitoring (28).

Methods to maintain the performance of brand products are issues that emerged in the program. The monitoring identified several brand products that show dissolution profiles markedly different from the original and/or with large variation between batches. A recent increase in the changes of API suppliers and formulation manufacturing sites, particularly after their patent expiration, should also increase the risk of performance change. The brand products are, however, outside the scope of the formulation

improvement in the current program. Optimizing the monitoring system (e.g., testing methods) and avoiding a significant increase in regulatory burden are other challenges to efficiently run the program.

8. Declaration of interests

This study was sponsored by the Japan Agency for Medical Research and Development (AMED) under Grant Numbers 19ak0101074j0103 and 19mk0101130j0001.

References

1. FDA. Guidance for Industry: Immediate release solid oral dosage forms, scale-up and postapproval changes: chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation. (1995).
2. MHLW. Guideline for bioequivalence studies of generic products (revision). (2012).
3. MHLW. Guideline for bioequivalence studies of generic products for different strengths of oral solid dosage forms (revision). (2012).
4. EMA. Guideline on the investigation of bioequivalence. (2010).
5. B. Davit, A.C. Braddy, D.P. Conner, and L.X. Yu. International guidelines for bioequivalence of systemically available orally administered generic drug products: a survey of similarities and differences. *AAPS J.* 15:974-990 (2013).
6. R. Kuribayashi, T. Takishita, and K. Mikami. Regulatory considerations of

- bioequivalence studies for oral solid dosage forms in Japan. *J Pharm Sci*:2270-2277 (2016).
7. FDA. Guidance for Industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. (2017).
 8. J.O. Sullivan, K. Blake, M. Berntgen, T. Salmonson, and J. Welink. Overview of the European Medicines Agency's development of product-specific bioequivalence guidelines. *Clin Pharmacol Ther* 104:539-545 (2018).
 9. FDA. Guidance for Industry: Bioavailability and bioequivalence studies submitted in NDAs or INDs—General considerations (draft guidance). (2014).
 10. ICH. Technical and regulatory considerations for pharmaceutical product lifecycle management (2017).
 11. H. Shibata, H. Yoshida, K. Izutsu, C. Yomota, Y. Goda, and H. Okuda. Scientific and regulatory approaches to confirm quality and improve patient perceptions of generic drug products in Japan. *AAPS Open*. 2:6 (2016).
 12. L.X. Yu. Pharmaceutical quality by design: product and process development, understanding, and control. *Pharm Res* 25:781-791 (2008).
 13. P.A. Dickinson, W.W. Lee, P.W. Stott, A.I. Townsend, J.P. Smart, P. Ghahramani, T. Hammett, L. Billett, S. Behn, R.C. Gibb, and B. Abrahamsson. Clinical relevance of dissolution testing in quality by design. *AAPS J* 10:380-390 (2008).
 14. J. Kushner, B.A. Langdon, I. Hicks, D. Song, F. Li, L. Kathiria, A. Kane, G. Ranade, and K. Agarwal. A quality-by-design study for an immediate-release tablet platform: examining the relative impact of active pharmaceutical ingredient properties, processing methods, and excipient variability on drug product quality

- attributes. *J Pharm Sci.* 103:527-538 (2014).
15. M. Panzitta, M. Ponti, G. Bruno, G. Cois, A. D'Arpino, P. Minghetti, F.R. Mendicino, L. Perioli, and M. Ricci. The strategic relevance of manufacturing technology: An overall quality concept to promote innovation preventing drug shortage. *Int J Pharm.* 516:144-157 (2017).
 16. K. Korasa and F. Vrečer. Overview of PAT process analyzers applicable in monitoring of film coating unit operations for manufacturing of solid oral dosage forms. *Eur J Pharm Sci* 111:278-292 (2018).
 17. M.J. Lee, D.Y. Seo, H.E. Lee, I.C. Wang, W.S. Kim, M.Y. Jeong, and G.J. Choi. In line NIR quantification of film thickness on pharmaceutical pellets during a fluid bed coating process. *Int J Pharm.* 403:66-67 (2011).
 18. EMA. Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action. (2017).
 19. FDA. Guidance for Industry: Dissolution testing of immediate release solid oral dosage forms. (1997).
 20. FDA. Guidance for Industry: Dissolution testing and acceptance criteria for immediate-release solid oral dosage form drug products containing high solubility drug substances. . (2018).
 21. A. Abend, T. Heimbach, M. Cohen, F. Kesisoglou, X. Pepin, and S. Suarez-Sharp. Dissolution and translational modeling strategies enabling patient-centric drug product development: the M-CERSI workshop summary report. *AAPS J.* 20:60 (2018).
 22. A. Hermans, A.M. Abend, F. Kesisoglou, T. Flanagan, M.J. Cohen, D.A. Diaz, Y. Mao, L. Zhang, G.K. Webster, Y. Lin, D.A. Hahn, C.A. Coutant, and H. Grady.

- Approaches for establishing clinically relevant dissolution specifications for immediate release solid oral dosage forms. *AAPS J* 19:1537-1549 (2017).
23. X. Zhang and R.A. Lionberger. Modeling and simulation of biopharmaceutical performance. *Clin Pharmacol Ther.* 95:480-482 (2014).
 24. C. Xu, M. Zou, Y. Wang, Y. Liu, J. Yan, Y. Wu, and G. Cheng. Discriminatory dissolution method for quality control measurements of carbamazepine immediate release tablets based on in vitro--in vivo investigations. *Drug Dev Ind Pharm.* 38:679-688 (2012).
 25. H. Yoshida, H. Shibata, K. Izutsu, and Y. Goda. Comparison of dissolution similarity assessment methods for products with large variations: f2 statistics and model-independent multivariate confidence region procedure for dissolution profiles of multiple oral products. *Biol Pharm Bull.* 40:722-725 (2017).
 26. MHLW. Guideline for bioequivalence studies for formulation changes of oral solid dosage forms (revision). (2012).
 27. Expert Committee on Quality of Generic Drug Products Homepage (in Japanese). <http://www.nihs.go.jp/drug/ecqaged.html>.
 28. B. Hens, Y. Tsume, M. Bermejo, P. Paixao, M.J. Koenigsnecht, J.R. Baker, W.L. Hasler, R. Lionberger, J. Fan, J. Dickens, K. Shedden, B. Wen, J. Wysocki, R. Loebenberg, A. Lee, A. Frances, G. Amidon, A. Yu, G. Benninghoff, N. Salehi, A. Talattof, D. Sun, and G.L. Amidon. Low buffer capacity and alternating motility along the human gastrointestinal tract: implications for in vivo dissolution and absorption of ionizable drugs. *Mol Pharm.* 14:4281-4294 (2017).

Figures and Tables

Fig. 1. Schematic figure of product lifecycles and bioequivalence tests.

Fig. 2. Dissolution profiles of spironolactone tablets (25 mg) obtained in four test media (H₂O and buffer solutions at pH 1.2, 4.0, and 6.8). Lines show those of the reference brand (current, Orange Book) and 12 generic formulations.

Fig. 3. Dissolution profiles of glimepiride orodispersible tablets (1 mg) obtained in four test media (H₂O and buffer solutions at pH 1.2, 4.0, and 6.8). Lines show those of the reference brand (current, Orange Book) and 7 generic formulations.

Fig. 4. Dissolution profiles of atenolol tablets (50 mg) obtained in three buffer solutions (pH 1.2, 4.0, and 6.8) in 2012 and 2014. Lines show those of the reference brand (current, Orange Book) and a generic formulation.

Table 1. Similarity parameters comparing the dissolution profiles applied by the Working Group of the ECQGDP.

Table 1. Acceptance criteria for similarity of dissolution profiles in Japanese BE guideline and ECQGDG working group

Average dissolution of reference product	Similarity criteria	
	BE Guideline	ECQGDG working group
(1) $\geq 85\%$ in 15 min	$\pm 15\%$ at 15 min	$\pm 20\%$ at 15 min
(2) $\geq 85\%$ in 15-30 min	i) $\pm 15\%$ at two time point ii) $f_2 \geq 42$	i) $\pm 20\%$ at two time point ii) $f_2 \geq 35$
3-a. $\geq 85\%$ in specified testing time	i) $\pm 15\%$ at two time point ii) $f_2 \geq 42$	i) $\pm 20\%$ at two time point ii) $f_2 \geq 35$
(3) $< 85\%$ at 30 min	3-b. 50-85% in specified testing time i) $\pm 12\%$ at two time point ii) $f_2 \geq 46$	i) $\pm 16\%$ at two time point ii) $f_2 \geq 42$
	3-c. $< 50\%$ in specified testing time i) $\pm 9\%$ at two time point ii) $f_2 \geq 53$	i) $\pm 12\%$ at two time point ii) $f_2 \geq 46$

Dissolution similarity is assured if either criterion i) or ii) is satisfied.

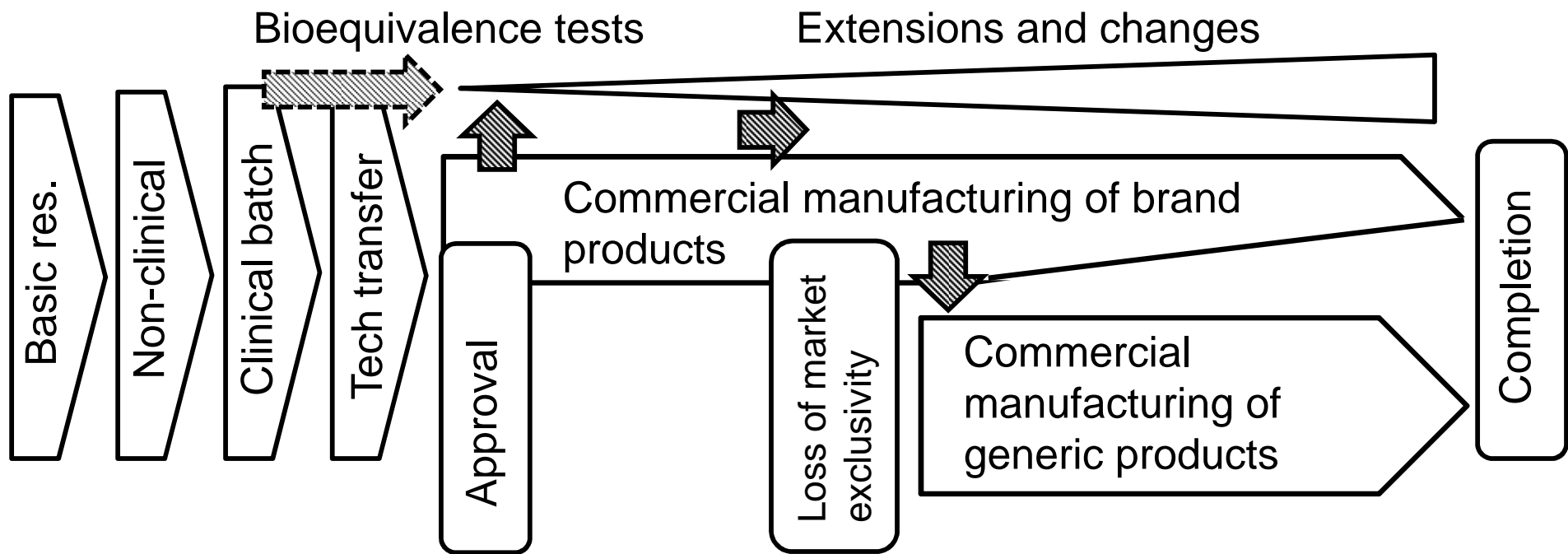


Figure 1

Fig. 3. Dissolution profiles of glimepiride orodispersible tablets (1 mg) obtained in four test media (H₂O and buffer solutions at pH 1.2, 4.0, and 6.8). Lines shows those of reference brand (current, orange book) and 7 generic formulations, respectively.

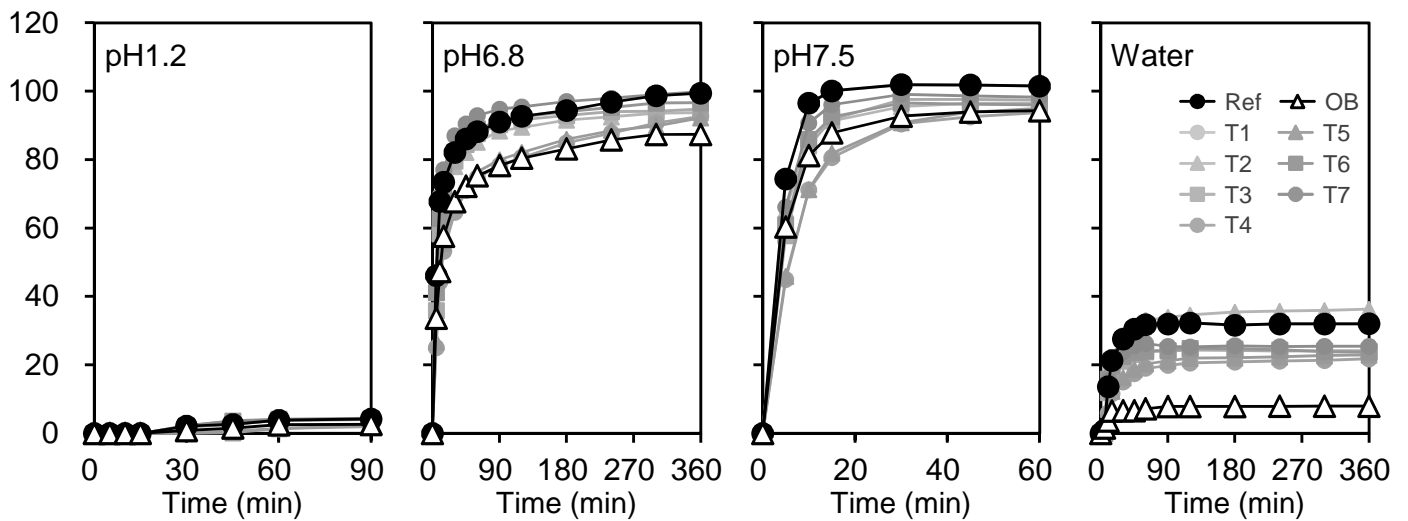
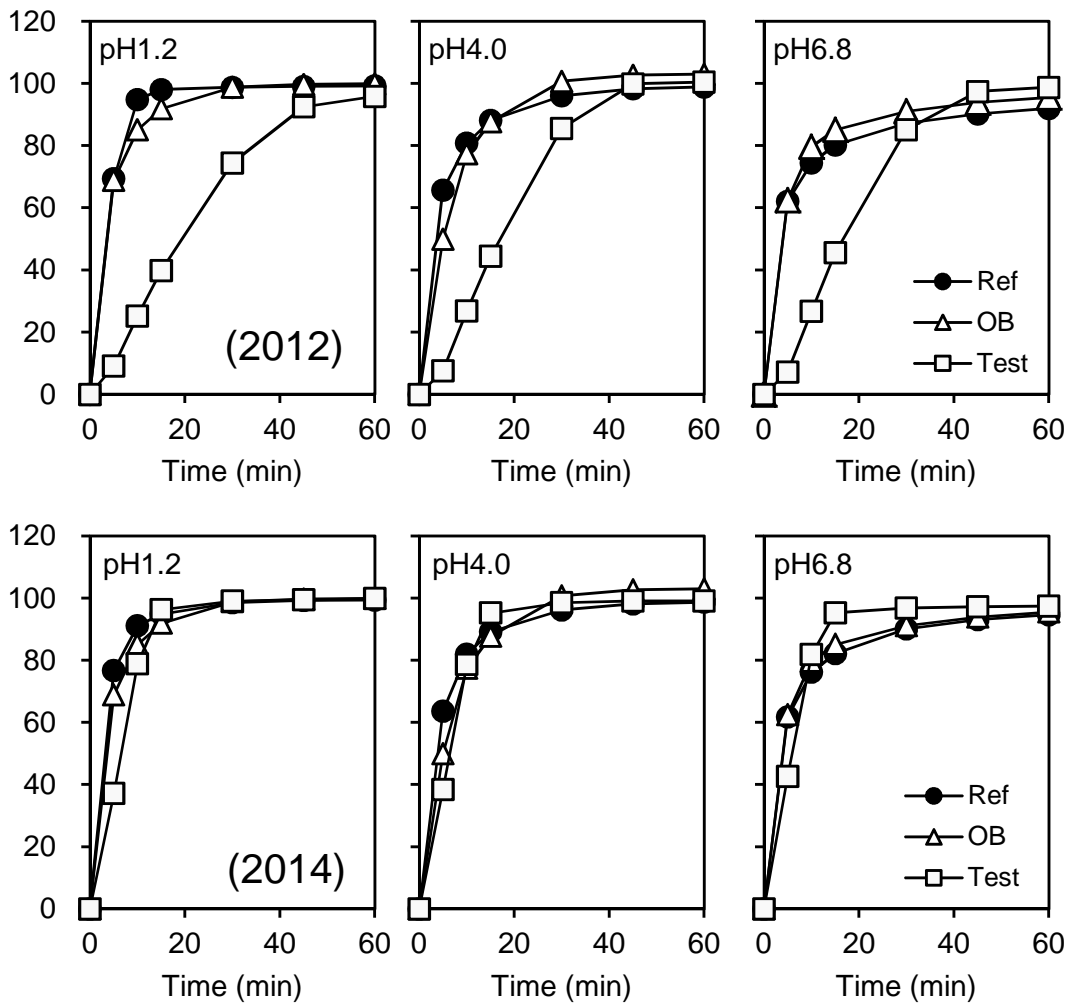


Fig. 4. Dissolution profiles of atenolol tablets (50 mg) obtained in three buffer solutions (pH 1.2, 4.0, and 6.8) in 2012 and 2014. Lines shows those of reference brand (current, orange book) and a generic formulation, respectively.



Conflict of Interests (COI)

The authors are members of Formulation Evaluation Working Group of the Expert Committee on Quality of Generic Drug Products (ECQGP). The study was sponsored by Japan Agency for Medical Research and Development (AMED) under Grant Number 19ak0101074j0103 and 19mk0101130j0001.

The authors declare that they have no competing interests.

Journal Pre-proof