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Review Article

Theme: Celebrating Women in the Pharmaceutical Sciences
Guest Editors: Diane Burgess, Marilyn Morris and Meena Subramanyam

FDA's Poly (Lactic-Co-Glycolic Acid) Research Program and Regulatory Outcomes

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Abstract. Poly (lactic-co-glycolic acid) (PLGA) has been used in many long-acting drug formulations which have been approved by the US Food and Drug Administration (FDA). However, generic counterparts for PLGA products have yet to gain FDA approval due to many complexities in formulation, characterization, and evaluation of test products. To address the challenges of generic development of PLGA-based products, the FDA has established an extensive research program to investigate novel methods and tools to aid both product development and regulatory review. The research focus have been: (1) analytical tools for characterization of PLGA polymers; (2) impacts of PLGA characteristics and manufacturing conditions on product performance; (3) *in vitro* drug release testing and *in vitro-in vivo* correlation of PLGA-based products, and (4) modeling tools to facilitate formulation design and bioequivalence study design of PLGA-based drugs. This article provides an overview of FDA's PLGA research program and highlights scientific accomplishments as well as regulatory outcomes that have resulted from successful research investigations.

KEY WORDS: bioequivalence; generic drugs; long-acting drugs; poly (lactide-co-glycolide); regulatory science.

INTRODUCTION

Poly (lactide-co-glycolide) (PLGA) is a biodegradable polymer that is used in most long-acting formulations approved by the FDA. PLGA is used to provide sustained release of drug in various long-acting formulations such as microspheres, *in situ* gel implants, and solid implants. Long-acting formulations offer many advantages compared to conventional formulations which contain the same active ingredients. Some advantages of sustained release formulations include: reduced dosing frequency, decreased incidence of side effects, maintenance of stable plasma concentrations, and better patient compliance.

More than 20 PLGA-based drug products have been approved by the FDA to date, with the first PLGA-based product approval occurring back in January 1989. Despite the increasing popularity and widespread use, there have not been any approvals for generic PLGA-based drug products in the USA. Compared to the development of generic conventional formulations, the overall costs of developing generic long-acting PLGA-based drug products are much higher and the risk of failure is also significantly greater. The main challenges associated with development of generic PLGA-based drug products are: (1) lack of full understanding of the impact of critical formulation and manufacturing parameters on product performance, (2) lack of compendial *in vitro* drug release testing (IVRT) methods that can discriminate formulations with manufacturing differences and predict *in vivo* performance, and (3) complicated bioequivalence study designs because of long application durations and complex multi-phasic *in vivo* pharmacokinetic (PK) profiles.

In 2013, the FDA issued two grant opportunities requesting proposals to investigate the *in vitro-in vivo* correlation (IVIVC) of parenteral microsphere [1] and ocular implant drug products [1]. FDA eventually awarded three grants that year to support research that would help determine bioequivalence study recommendations for generic microsphere and implant drug products. Through these studies, it was apparent that while the establishment of an IVIVC would be helpful for determining clinically relevant dissolution conditions, many other questions surrounding the

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PLGA polymers that are used to achieve long-term drug release from microspheres and implants would need to be explored.

FDA has continued to award research projects each year through grants and contracts and a research program to address scientific gaps on long-acting formulations was established. To date, more than eight grants and nine contracts have been awarded and two internal projects were initiated at the FDA to investigate PLGA-based drug products. This article builds on a prior publication [2] which describes the PLGA research program established by the FDA and its outcomes since its inception.

BIOEQUIVALENCE RECOMMENDATIONS: REQUIREMENTS AND CHALLENGES

Bioequivalence study recommendations are outlined in Product-Specific Guidances (PSGs) that are posted for each Reference Listed Drug (RLD) [3]. In general, for PLGA-based products, the main recommendations include: (1) qualitative and quantitative (Q1/Q2) formulation sameness, (2) comparative *in vitro* release testing (IVRT), and (3) a comparative *in vivo* study.

Q1/Q2 Sameness

It is recognized that the PLGA polymer that constitutes the microsphere/implant vehicle contributes significantly to drug release. Characteristics of PLGA such as the monomer ratio, molecular weight, and polymer structure can vastly alter the drug release mechanism and release rate. By regulation, generic PLGA-based injectable microspheres/implants need to be qualitatively (Q1) and quantitatively (Q2) the same to the corresponding RLD.[1] However, as a random copolymer, the inherent heterogeneity associated with PLGA makes assessment of Q1 sameness of PLGA very challenging.

To aid in the assessment of Q1 sameness of PLGA, information on PLGA characteristics such as the polymer composition (the ratio between glycolic acid and lactic acid), molecular weight (MW) and weight distribution, and PLGA architecture (e.g., linear or star-branched PLGA) are needed [4]. In addition, considering PLGA characteristics can be altered during manufacturing, the Q1 sameness of PLGA is assessed based on characteristics of the PLGA extracted from the finished generic product rather than the raw PLGA prior to processing. In terms of acceptance criteria for determining Q1 sameness of PLGA, there are not universal standards that cover all PLGA-based injectable/implantable products. That being said, the PLGA in a proposed generic product is generally expected to have the same polymer structure and very similar polymer composition. Besides the polymer composition, MW, and polymer structure, other PLGA characteristics including, but not limited to, glass transition temperature and intrinsic/inherent viscosities are also important for product performance. Therefore, additional data on PLGA characterization may be requested during the substantive assessment of a particular generic drug application, which is submitted as an abbreviated new drug application (ANDA). The final acceptability ultimately depends on data provided by an ANDA applicant to show the PLGA used in the proposed generic product would be able to provide comparable drug release kinetics and duration to the reference product.

[1] 21 CFR 314.94(a)(9)(iii)

IVRT

IVRT is useful for evaluating the effect of manufacturing differences and to assess performance characteristics of sustained release dosage forms such as PLGA-based drug products. Q1/Q2 sameness does not necessarily lead to comparable product performance since PLGA-based microspheres/implants are very sensitive to manufacturing conditions. Minor differences in manufacturing process may result in significant changes in drug release kinetics and bioavailability. An *in vitro* release rate reflects the combined effect of several physical and chemical parameters and IVRT is used as one of the routine performance testing tools to characterize the performance characteristics of a sustained release drug product.

Since real-time release testing of many PLGA-based products require extended periods of time, accelerated release testing can also be conducted to provide fast quality assessment and facilitate product development when it is properly validated to be reproducible and discriminatory. In addition, when an accelerated release testing is shown to correlate with real-time release and/or *in vivo* drug release, it may also be used for establishing bioequivalence of a proposed generic long-acting drug [4].

Comparative *In Vivo* Study

Table I below summarizes the different studies that are recommended for Product-Specific Guidances (PSGs) for PLGA-based drug products that have been posted to date. As shown, a comparative *in vivo* study is recommended in all posted PSGs. Depending on the drug product, the *in vivo* study may be a comparative clinical endpoint study or a pharmacokinetic (PK) study conducted in either patients or healthy subjects. When the PSG recommends a PK study to demonstrate BE, it generally recommends single dose, parallel design in healthy subjects. But sometimes, due to safety consideration, the use of healthy subjects may not be feasible for some products (e.g., risperidone injectable microspheres). In such cases, the PSG may recommend the study be conducted in patients who the drug product is intended to treat. In addition, considering the unique multi-phasic *in vivo* drug release behavior of PLGA-based drug products, the PSG may recommend partial AUC (area under the plasma concentration time curve) metrics in addition to the conventional metrics of Cmax (peak plasma concentration) and AUC to ensure comparable sustainability between a proposed generic product and the RLD. When the safety profile of the drug product suggests using patients who are already receiving the drug, a steady-state study is recommended to establish BE without disrupting a patient's ongoing treatment. For a steady-state PK study, appropriate sampling should be conducted to document the attainment of steady-state.

Table I. Product-Specific Bioequivalence Recommendations on PLGA-Based Products

Active ingredient	Dosage form	Bioequivalence study type	Partial AUC recommendation
Buprenorphine	Solution	Comparative single-dose *in vivo* study in patients with PK endpoints	Y
Goserelin acetate	Implant		N
Leuprolide acetate	Injectable		Y
Leuprolide acetate; norethindrone acetate	Injectable, tablet		Y
Triptorelin pamoate	Injectable		Y
Naltrexone	For suspension	Comparative single-dose *in vivo* study in healthy general population with PK endpoints	Y
Octreotride acetate	Injectable		Y
Risperidone	Injection	Two studies: (1) comparative *in vitro* drug release testing, (2) comparative multiple-dose, steady-state *in vivo* study in patients with PK endpoints	N
Mincocycline hydrochloride	Powder	Comparative *in vivo* study with clinical endpoints	N/A

Advancing Bioequivalence Recommendations

The prolonged and multi-phasic drug release behavior of PLGA-based drugs and its sensitivity to minor formulation and manufacturing changes makes generic development very challenging. Although PSGs for some PLGA-based drugs have been posted and more are under development [5], it is recognized that there are still remaining scientific gaps in this area, such as polymer and formulation characterization, IVRT, and optimization of the *in vivo* study design using modeling and simulation tools. But this also means that there are opportunities to advance the current understanding of PLGA-based drugs and their behavior both *in vitro* and *in vivo* and exploring novel alternative approaches through various research projects.

FDA'S PLGA RESEARCH PROGRAM

FDA launched a research program for PLGA-based drug products in 2013 supported by funding from the Generic Drug User Fee Amendments (GDUFA). The research program is implemented by the Office of Generic Drugs (OGD) and includes both external research projects (awarded to industry, academia, and other government agencies) and internal collaborations to address scientific gaps that exist during generic drug development and regulatory review. Over the years, the program has grown to encompass the following research areas: (1) new analytical methods for characterizing PLGA polymers and PLGA-based formulations; (2) novel IVRT methods and IVIVC of PLGA-based drugs; (3) investigation of the impact of variation in raw materials and manufacturing on drug release characteristics and drug polymer interactions, and (4) new modeling tools to facilitate formulation design and bioequivalence study design of PLGA-based drugs. Significant progress has been made in each of these research areas and studies results have been shared through peer-reviewed publications and meeting abstracts/posters. Some highlights from the first three areas are described below. Research on new modeling tools is still in its initial stages and findings have yet to be shared publicly.

Characterization of PLGA Polymers

Accurate characterization of the PLGA polymer is critical for development of generic PLGA-based products in terms of reverse engineering, establishment of Q1/Q2 sameness, and quality control of the raw polymer and the finished drug product. Through the GDUFA research program, FDA has funded several research projects to develop advanced analytical methods to characterize PLGA polymers.

In one project, procedures to extract PLGA from commercial drug products and analytical methods for several key characteristics of PLGA polymer, including MW, weight distribution, lactic acid to glycolic acid (L/G) ratio, and end cap analysis, were successfully established [6]. In addition to these characteristics, polymer structure is another critical polymer attribute that can impact product performance. The structure of the PLGA polymer can either be linear or branched (e.g., star-shaped). Given that there were no readily available methods for structure analysis of branched-PLGA polymers, a research project was developed to fill this gap. To this end, an analytical method based on gel-permeation-chromatography (GPC) with quadruple detection systems was developed and validated using in-house synthesized branched-PLGA standards [7]. This method was also used to elucidate the branch units of polymers extracted from Sandostatin® LAR and several star-shaped glucose-PLGA polymers obtained from different vendors. The outcome of this project provides valuable support to regulatory activities, and it will continue to benefit generic drug development of star glucose-PLGA polymer-based products.

To achieve desired drug release kinetics and application duration, a drug product may contain a mixture of different PLGA polymers. This type of formulation design makes it extremely challenging to characterize PLGA polymers due to the difficulty to separate one from the other, especially for PLGAs with similar molecular weight and/or different L/G ratio. To overcome this challenge, a research project was conducted to develop methods to separate PLGAs with different lactide content based on the solubility difference in different solvents [8]. After screening a large number of solvents, it was identified that a group of solvents (so-called semi-solvents) tends to dissolve polymer of high lactide

content, showing promise to separate polymer blend of different L/G ratio [9]. A protocol using sequential treatment of selected semi-solvents was able to separate PLGA polymers in Trelstar® into fractions of distinct L/G ratio.

Development of IVRT Methods and IVIVCs for PLGA Microspheres

Research projects to develop IVRT methods and IVIVCs of PLGA-based products have produced 10 publications: five on IVIVCs of four different active pharmaceutical ingredient (API) microsphere formulations, two on developing accelerated and real-time *in vitro* drug release methods, and three on mechanistic analysis of drug release from microsphere formulations.

Prior to the published IVIVCs, limited data were available on IVIVC of PLGA-based microsphere formulations [10, 11]. Through FDA's research program, IVIVCs for PLGA microspheres containing risperidone, naltrexone [12, 13], triamcinolone acetonide [14], and leuprolide acetate [15, 16] were explored using a rabbit or rat model. A cage implant system for assessing *in vivo* performance of PLGA-based microspheres was developed and validated [17]. PLGA microspheres containing triamcinolone acetonide or leuprolide acetate were used as model products. Pharmacokinetics (PK) in rats was assessed after subcutaneous injection or subcutaneous in-cage implantation of microspheres. PK profiles with and without the cage were highly similar during the 2- to 3-week release duration, which provides a simple means to recover and evaluate the microsphere drug carriers *in vivo*. This approach is useful to obtain better understanding on release mechanisms and polymer erosion *in vivo*, which may enable developing more biorelevant IVRT methods to facilitate development of mechanism-based IVIVC.

While evaluating IVIVCs of PLGA microspheres, it was recognized that it is particularly challenging to correlate the initial burst release phase *in vitro* and *in vivo*. Accordingly, additional efforts were made to better understand the effect of variable burst release on IVIVC of PLGA microspheres [10]. Data on microspheres containing risperidone or leuprolide acetate was reported for the first time [11]. It was observed that IVIVCs developed using formulations with less variation in burst release had better predictability and vice-versa. Although the IVIVCs were established using animal data, these results laid the groundwork that allowed future investigations into clinical IVIVC development and also IVIVC development for other microsphere products.

In addition to developing IVIVC, IVRT was also used as a powerful tool to investigate the impact of manufacturing conditions and IVRT methods on drug release mechanisms *in vitro* [18]. The *in vitro* evaluation of leuprolide acetate loaded microspheres indicated that the *in vitro* drug release mechanisms are very complex. It was hypothesized that the release mechanisms of leuprolide-loaded PLGA microspheres may involve (1) polymer erosion (mass loss); (2) diffusion of peptide and pore healing in early phase; (3) water mediated release, and (4) peptide desorption from the polymer matrix (peptide PLGA interactions). All these mechanisms are largely interrelated and the experimental testing conditions, such as release media composition, may affect the level of contribution from each potential mechanism on drug release.

Impact of Variation in Raw Materials and Manufacturing

While developing IVRT methods for PLGA-based formulations, it was recognized that variation in raw materials and manufacturing may have significant impact on the physicochemical characteristics and drug release behavior of the finished formulation [19]. Accordingly, several projects were developed to systematically investigate and determine the impact of variation in raw material and manufacturing on product performance. In general, a commercial product is selected to serve as the reference product whenever feasible. Reverse engineering of the commercial product was conducted to provide more guidance on developing in-house formulations with difference in either formulation composition or manufacturing process. Complete or partial data on reverse engineering of commercial products and related analytical methods have been reported for several commercial products including PLGA microspheres containing risperidone, naltrexone, leuprolide acetate, triptorelin pamoate, or octreotide [6, 7, 9, 12, 20]. As previously mentioned, a generic PLGA-based injectable formulation is required to be Q1/Q2 the same as the reference product. Thus, the reports on reverse engineering of reference products could be helpful to facilitate generic development and review by providing information on key polymer characteristics of PLGA for supporting Q1/Q2 assessment and related characterization methods.

When considering impact of PLGA characteristics on drug release, in general, microspheres made of PLGA with larger MW and/or higher L/G ratio should provide longer drug release duration in theory. However, the impact of PLGA MW on drug release can be complicated as the impact of MW may not always follow the same general trend. In the case of risperidone-loaded microspheres, it is known that risperidone is an amine drug which acts as catalyst for PLGA degradation thus making the impact of PLGA MW on drug release less predictable. A study was conducted to better understand the effect of PLGA MW differences on risperidone release from microspheres [21]. It was interesting to observe that the *in vitro* release profiles did not follow the general trend of the MW of the PLGA used. The catalytic effect of risperidone on PLGA during manufacturing and release testing may be responsible for the observation as it minimized the differences in MW of the formulations.

To determine variation among different material sources and its potential impact on the formulation characteristics, microspheres with the "same" composition were prepared using the "same" PLGA obtained from different sources [22]. It was observed that minor difference in characteristics of raw materials (i.e., molecular weight: up to 15.1 kDa from 13.9 kDa) resulted in noticeable changes in encapsulation efficiency and particle size of the formulation. The study results indicate that physicochemical properties (drug loading, particle size, porosity) and *in vitro* release characteristics of microspheres (i.e., initial burst release) can be sensitive to the source of the polymers and manufacturing conditions.

The obtained knowledge on the impact of raw material and manufacturing could be helpful for facilitating generic

development of PLGA-based products. It is important to keep these potential impacts in mind when conducting reverse engineering of the reference product and designing formulation composition and manufacturing for generic products. The characteristics of the PLGA in the final product may be significantly different from the characteristics of the starting PLGA depending on the manufacturing conditions.

REGULATORY RESEARCH OUTCOMES

Research conducted through the GDUFA program support (1) the development of generic drug products, (2) the generation of evidence needed to support efficient review and timely approval of ANDAs, and (3) the evaluation of generic drug equivalence [23, 24]. Scientific results from GDUFA research projects are intended to help FDA reviewers evaluate generic drug equivalence and for industry to successfully develop new generic products. Examples of outcomes from research include improved understanding of product characteristics, development of an analytical method, design of a laboratory test, implementation of a predictive model, or validation of a statistical approach.

Research outcomes that support the development of generic drug products prior to ANDA submission may contribute towards review of pre-ANDA meetings, Controlled Correspondences, and development of PSGs and general guidances. Research outcomes that support the generation of evidence needed to support efficient review and timely approval of ANDAs can impact number of ANDA submissions for a particular drug product as well as the eventual ANDA reviews and approvals for that product. Research outcomes that support evaluation of generic drug equivalence are evidenced through PSGs that provide new approaches to equivalence, such as *in vitro* approaches that may be recommended in lieu of *in vivo* studies.

FDA's PLGA research program has made significant regulatory impact. Prior to the launch of the PLGA research program, there were no PSGs that provided recommendations on PLGA characterization and no recommendations were provided for evaluation of Q1 sameness of PLGA polymers. With the knowledge obtained from projects focusing on characterizing PLGA polymers, in May 2015, the PSG for risperidone injectable microspheres was revised to provide guidance on specific PLGA characterization data needed for a Q1 sameness assessment [4]. The additional recommendations on PLGA characterization have provided greater clarity to generic companies seeking to develop generic PLGA-based products. Prior to the PSG revision, very few Controlled Correspondences requesting Q1/Q2 formulation assessment of PLGA products were submitted to the Agency. Since the PSG revision, more than 155 Controlled Correspondences for assessing Q1/Q2 sameness of PLGA-based drug products have been submitted to date, indicating that additional guidance on Q1 sameness of PLGA may have provided greater understanding to generic industry on how FDA evaluates PLGA-based formulations.

In addition, a publication which resulted from an FDA-funded grant which describes an analytical protocol of characterizing molecular weight/weight distribution, monomer ratio, and end group [6] was published in 2015. This article has been widely cited by generic companies in various regulatory submissions, demonstrating its importance in providing key information to successfully perform reverse engineering of PLGA-based reference products.

Another regulatory outcome relates to improved IVRT methods for PLGA-based products. Significant research effort in establishing IVIVCs of PLGA-based products led to optimization of IVRT methods for microspheres for both real-time and accelerated drug release [1, 11, 12, 16]. Accelerated drug release methods for microspheres may also be adopted for quality control of the drug product. Accelerated release profiles were found to correlate with real-time release profiles, and these methods are also helpful for formulation screening during the early development phase. The different release profiles of Q1/Q2 microsphere formulations confirmed the sensitivity of this dosage form to changes in manufacturing conditions [11, 13, 16]. The identified critical formulation and manufacturing parameters are important for setting proper regulatory review standards and to guide generic drug product development. The scientific knowledge gained from these projects has been utilized to review controls and pre-ANDA meeting requests.

The number of pre-ANDA meeting requests on PLGA-based drug products has also steadily increased since the start of the PLGA research program. Pre-ANDA meetings can be requested by an applicant to discuss scientific issues or questions relating to an ongoing ANDA development program [25]. Pre-ANDA meetings support the identification and discussion of challenging questions relating to Q1/Q2 sameness, PLGA characterization, testing methods, and *in vivo* study design. Results from the PLGA research program have informed FDA in preparing responses to scientific questions received through pre-ANDA meeting requests. This has helped applicants by providing guidance and scientific understanding to address hurdles in generic drug development of PLGA-based products.

Results from research have also been shared and discussed with the scientific community through public workshops and global pharmaceutical conferences. For example, in 2017, the FDA organized a complex drug workshop to discuss strategies for demonstrating equivalence of generic complex drug substances and formulation. Session II of this workshop focused on characterization of PLGA polymers and PLGA-based formulations. Key findings of the GDUFA funded internal and external research projects were highlighted in the workshop. To follow on from the 2017 public workshop, the FDA and the Controlled Release Society (CRS) co-sponsored a workshop, namely, "Equivalence of complex long-acting drugs workshop," during the 2020 CRS Annual Meeting & Exposition [26]. This full day workshop covered topics in four areas including (1) regulatory challenges and scientific initiatives; (2) technologies for characterization of raw materials and formulations; (3) *in vitro* drug release testing and *in vitro-in vivo* correlation, and (4) modeling and simulation strategies. These workshops and conferences provide a useful platform for the FDA to exchange scientific and regulatory thinking and collaborate with scientists from academia, pharmaceutical industry, and the other regulatory agencies.

FUTURE DIRECTIONS

In the 7 years since the start of the PLGA research program, there have been significant advances in understanding PLGA polymer characteristics and tests that should be performed to properly assess *in vitro* and *in vivo* performance. Results from the PLGA research program have demonstrated that different manufacturing processes could produce microspheres with different characteristics (i.e., internal structure and surface properties) even when the formulation composition is Q1/Q2 the same [27]. These differences may have *in vivo* performance and safety implications. How to fully characterize these differences and their impact on product efficacy and safety remains to be addressed.

While IVIVCs have been successfully developed for small molecules and peptides in animal models, it would be beneficial to establish IVIVCs in humans using improved IVRT methods. In addition, for peptide-loaded PLGA formulations (i.e., microspheres, *in situ* forming, and/or solid implants), research is needed to investigate the impact of peptide-PLGA interactions on safety.

Quantitative clinical pharmacology tools are being investigated to support the evaluation of alternative comparative clinical endpoint study designs for PLGA-based drugs. Considering the challenges in conducting BE studies due to their long duration and high dropout rate for many of these products, alternatives in study design to shorten the duration or supplement simpler study designs with predictive modeling are being explored.

As interest in development of PLGA-based drug products continues to grow, FDA will seek to maintain a scientifically strong research program to address questions raised from review of regulatory submissions and to advance new and improved methods for product assessment.

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REFERENCES

1. In vitro-in vivo correlations of ocular implants (U01). 2013 [7/22/20]; Available from: https://grants.nih.gov/grants/guide/rfa-files/rfa-fd-13-029.html.
2. Wang Y, Qu W. Choi S. American Pharmaceutical Review: FDA's regulatory science program for generic PLA/PLGA-based drug products; 2016.
3. CDER/FDA. Product-specific guidances for generic drug development 2020 [7/22]; Available from: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
4. CDER/FDA Draft guidance on Risperidone injectable intramuscular 2020 [7/27]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_R-V08-16%20separate%20post.pdf.
5. CDER/FDA. Upcoming product-specific guidances for complex generic drug product development (2020) [8/26]; Available from: https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development.
6. Garner J, Skidmore S, Park H, Park K, Choi S, Wang Y. A protocol for assay of poly(lactide-co-glycolide) in clinical products. J Pharm Sci. 2018, 107;(1):353–61. https://doi.org/10.1016/jxphs2017100272015.
7. Hadar J, Skidmore S, Garner J, Park H, Park K, Wang Y, et al. Characterization of branched poly(lactide-co-glycolide) polymers used in injectable, long-acting formulations. J Control Release. 2019;304:125–34. https://doi.org/10.1016/jjconrel2019050032019.
8. Park K, Skidmore S, Hadar J, Garner J, Park H, Otte A, et al. Injectable, long-acting PLGA formulations: analyzing PLGA and understanding microparticle formation. Int J Pharm. 2019;(565):447–57. https://doi.org/10.1016/jijpharm2019040522019.
9. Skidmore S, Hadar J, Garner J, Park H, Park K, Wang Y, et al. Complex sameness: separation of mixed poly(lactide-co-glycolide)s based on the lactide:glycolide ratio. Int J Pharm. 2019;(561):305–13. https://doi.org/10.1016/jijpharm2019030172019.
10. Andhariya JV, Jog R, Shen J, Choi S, Wang Y, Zou Y, et al. In vitro-in vivo correlation of parenteral PLGA microspheres: effect of variable burst release. AAPS PharmSciTech. 2020;20(8):320. https://doi.org/10.1208/s12249-019-1508-72020.
11. Shen J, Choi S, Qu W, Wang Y, Burgess DJ. In vitro-in vivo correlation of parenteral Risperidone polymeric microspheres. Int J Pharm. 2016;498(1-2):274–82. https://doi.org/10.1016/jijpharm2015120312015.
12. Andhariya JV, Choi S, Wang Y, Zou Y, Burgess DJ, Shen J. Accelerated in vitro release testing method for naltrexone loaded PLGA microspheres. J Control Release. 2017;255:27–35. https://doi.org/10.1016/jjconrel2017033962017.
13. Andhariya JV, Shen J, Choi S, Wang Y, Zou Y, Burgess DJ. Development of in vitro-in vivo correlation of parenteral naltrexone loaded polymeric microspheres. Int J Pharm. 2018;549(1-2):109–14. https://doi.org/10.1016/jijpharm2018070192017.
14. Doty AC, Weinstein DG, Hirota K, Olsen KF, Ackermann R, Wang Y, et al. Mechanisms of in vivo release of triamcinolone acetonide from PLGA microspheres. Eur J Pharm Biopharm. 2016;113:24–33. https://doi.org/10.1016/jejpb2016110082017.
15. Hirota K, Doty AC, Ackermann R, Zhou J, Olsen KF, Feng MR, et al. Characterizing release mechanisms of leuprolide acteate loaded PLGA microspheres for IVIVC development I: in vitro evaluation. J Aerosol Sci. 2013;59:6–21. https://doi.org/10.1016/jjaerosci201301008.
16. Andhariya J, Jog R, Shen J, Choi S, Wang Y, Zou Y, et al. Development of level A in vitro-in vivo correlations for peptide loaded PLGA microspheres. Mol Pharm. 2019;16(8):3617–25. https://doi.org/10.1021/acsmolpharmaceut9b004552019.
17. Doty A, Hirota K, Olsen K, Sakamoto N, Wang Y, Choi S, et al. Validation of a cage implant system for assessing in vivo performance of long-acting relase microspheres. Pharm Res. 2013;29(11):3122–30. https://doi.org/10.1007/s11095-012-0804-72016.
18. Doty AC, Zhang Y, Weinstein DG, Wang Y, Choi S, Qu W, et al. Mechanistic analysis of triamcinolone acetonide release from PLGA microspheres as a function of varying in vitro release conditions. Biomaterials. 2016;109:88–96. https://doi.org/10.1016/jbiomaterials2016070412016.
19. Andhariya JV, Shen J, Wang Y, Choi S, Burgess DJ. Effect of minor manufacturing changes on stability of compositionally equivalent PLGA microspheres. J Pharm Sci. 2019;108(6):2002–11. https://doi.org/10.1016/jxphs2019010032019.
20. Zhou J, Hirota K, Ackermann R, Walker J, Wang Y, Choi S, et al. Reverse engineering the 1-month Lupron Depot(R). AAPS J. 2018;20(6):105. https://doi.org/10.1208/s12248-018-0253-2.

21. Kohno M, Andhariya J, Rothstein S, Wang Y, Qin B, Burgess D. The effect of PLGA molecular weight on drug release from microspheres. AAPS 2019. PharmSci. 2020;360, San Antonio, TX.
22. Zhou J, Walker J, Ackermann R, Olsen K, Hong JKY, Wang Y, et al. Effect of manufacturing variables and raw materials on the composition-equivalent PLGA microspheres for 1-month controlled release of leuprolide. Mol Pharm. 2020;17(5):1502–15. https://doi.org/10.1021/acs.molpharmaceut.9b01188.
23. FDA. GDUFA II Commitment Letter (2020) [7/30]; Available from: https://www.fda.gov/media/101052/download.
24. CDER/FDA. FY 2018 GDUFA Science and Research Outcomes (2020) [7/30]; Available from: https://www.fda.gov/drugs/generic-drugs/fy-2018-gdufa-science-and-research-outcomes
25. CDER/FDA. Formal Meetings Between FDA and ANDA Applicants of Complex Products (2020) Under GDUFA - Guidance for Industry. 2017 [8/26/20]; Available from: https://www.fda.gov/media/107626/download.
26. Equivalence of complex long acting drugs workshop (2020) Virtual Annual Meeting Vision for Global Impact Controlled Release Society.
27. Shen J, Lee K, Choi S, Qu W, Wang Y, Burgess DJ. A reproducible accelerated in vitro release testing method for PLGA microspheres. AAPS J. 2017;19(5):1396–410. https://doi.org/10.1208/s12248-017-0095-32016.