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# Complex Formulations – Main Considerations

## The way forward for complex formulations

FY 2020 Generic Drug Regulatory Science Initiatives
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# Disclaimer

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# Outline

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1. Current Guidance/ Recommendations by the Autorities
2. Open Questions – Gap Analysis
3. Basic Information for PLGA microspheres
4. The Importance of Case by Case Study
5. The Way Forward
6. Conclusions

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# The Case of PLGA microparticles

# Complex Formulations in PLGA micropsheres

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**What we know so far:**

- A lot of emphasis has been given to the comparative characterization of the PLGA polymers.

## Q1/Q2 assessment on generic PLGA products

FDA

- Provide comparative characterization data on PLGA polymer from the Generic and RLD
- Characterization should include, but is not limited to: composition (L/G ratio), molecular weight and molecular weight distribution, polymer structure (i.e., linear or star), inherent viscosity, glass transition temperature, and polymer end-cap
- Should characterize the branch frequency if it is a star polymer
- If there are differences, need to provide justification on why these differences would not impact the safety or efficacy of the generic drug as compared to the RLD

Source: Presentation from Bin Qin, PhD., Complex Generic Drug product Development Workshop, September 12, 2018

# Complex Formulations in PLGA micropsheres

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## What we know so far:

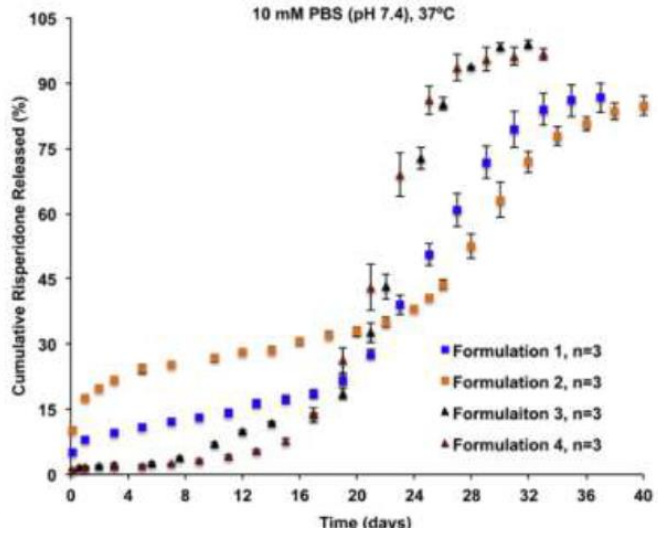
- The importance of the discriminatory ability of the IVRT method to support comparability with the reference product

## IVRT Method Validation

FDA

Validation components:

Selectivity/ Discriminatory Ability




Ability to discriminate the effect of process variability in the production of the test formulation.

www.fda.gov

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Source: Presentation from Yan Wang, Ph.D, Complex Generic Drug product Development Workshop, September 12, 2018

# Open Questions – Gap Analysis

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**Q: Is the provided information/guidance enough?**

**A:** The general information/guidance for PLGA characterization is not enough.

**Q: Why generics cannot still find their way through?**

**A:** 1) Each PLGA product is a different case & governed by different attributes.
2) Sameness in the manufacturing process.

**Q: How about the manufacturing process and the importance of it to achieve bioequivalence ?**

**A:** The manufacturing process plays a huge role in the final release profile. Minor differences in the manufacturing process can utterly alter the release profile.

**Q: What is the way forward?**

**A:** Case by case understanding of what <u>really</u> affects the release profile.

# Marketed Products in PLGA microspheres

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| Drug Product | Active Ingredient | Dosage Form, Route of Administration | Packaging System | Approval Date, Indication(s) |
|---|---|---|---|---|
| Zoladex | Goserilin acetate | Implant, SC | PFS | 1989 |
| Lupron Depot | Leuprolide acetate | PLGA, PLA Microspheres, IM | PFS Dual Chamber | 1990 |
| Lupron Depot-PED | Leuprolide acetate | PLGA, PLA Microspheres, IM | PFS Dual Chamber | 1993 |
| Lupron | Leuprolide acetate | PLGA Microspheres, IM | Vial (lyo powd) & ampule, (dil) | 1995 |
| Sandostatin LAR | Octerotide | PLGA Microspheres, SC | Vial (microsp) & PFS (dil) | 1998 |
| Trelstar | Triptorelin pamoate | PLGA Microspheres, IM | Vial (microsp) & PFS (dil) | 2000 & 2010 |
| Arestin | Minocycline HCl | PLGA Microspheres, Peridontal | Special unit dose cartridge | 2001 |
| Risperidal Consta | Risperidone | PLGA Microspheres, IM | Vial (microsp) & PFS (dil) | 2003 |
| Vivitrol | PLGA Microspheres, IM | PLGA Microspheres, IM | Vial (microsp) & Vial (dil) | 2006 |
| Ozurdex | Dexamethasone | PLGA Implant, Intra-vitreal | DDS Applicator | 2009 |
| Bydureon | Exenatide | PLGA Microspheres, SC | Dual chamber pen | 2012 |
| Lupaneta Pack | Leuprolide acetate, Norethindrone acetate | PLGA Microspheres - IM, Tablet - Oral | PFS Dual Chamber + Tablet | 2012 |
| Signifor LAR | Pasireotide pamoate | Microspheres, IM | Vial (microsp) & PFS (dil) | 2014 |
| ZILRETTA | Triamcinolone acetonide | Microspheres, Intrarticular | Vial (microsp) & Vial (dil) | 2017 |
| Byderon Bcise | Exenatide | PLGA Microspheres, SC | Single chamber pen | 2017 |

# Basic Information for PLGA microsphers

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**Looking closely in the previous list we can identify two main types of drugs.**

| Types of Drugs: | Hydrophilic | Hydrophobic |
|---|---|---|
| **Key Aspects:** | • Low drug loading; most of the times is close to 5%.<br>• Due to the low drug loading the active ingredient has no influence in the release profile.<br>• The release profile in this case is governed by:<br>*1.The polymer type e.g. star branched or linear, lactide to glycolide ratio, molecular weight etc.*<br>*2.The manufacturing process-technique e.g. double emulsification, coacervation* | • High drug loading; it can go up to 33-38%.<br>• Due to the high drug loading the active ingredient has big influence in the release profile**. Special consideration when drug is degrading the polymer.**<br>• The release profile in this case is governed by:<br>*1.The polymer type e.g. lactide to glycolide ratio, molecular weight etc.*<br>*2.The manufacturing process e.g. solvents to be used, duration of the steps, washing & drying of the micropsheres.*<br>*3.The physical properties of the encapsulated drug e.g. distribution of the drug, crystallinity Vs amorphous etc.* |

# The Importance of Case by Case Study

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## Why is not always the PLGA?

- Many companies have unsuccessfully attempted to develop a generic product of PLGA micropsheres, mainly by starting with the **same type of polymer** and altering the manufacturing process e.g. using different solvent (the more frequently used dichloromethane for example).

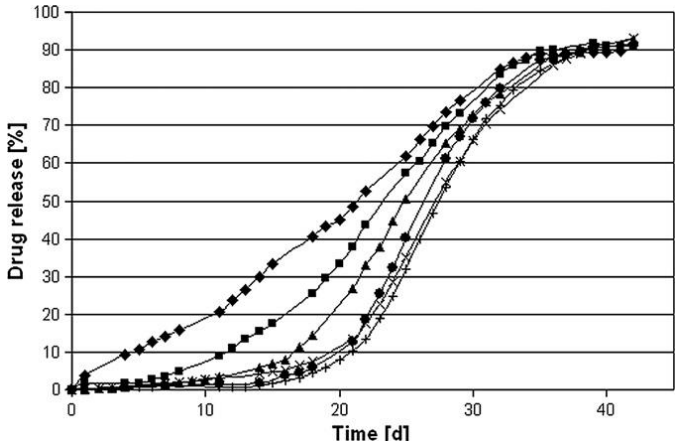


Fig. 7. Drug release profiles of the microspheres prepared at 10 °C (-♦-), 20 °C (-■-), 27.5 °C (-▲-), 30 °C (-×-), 32.5 °C (-+-), and 35 °C (-●-) (37 °C and pH 7.4).

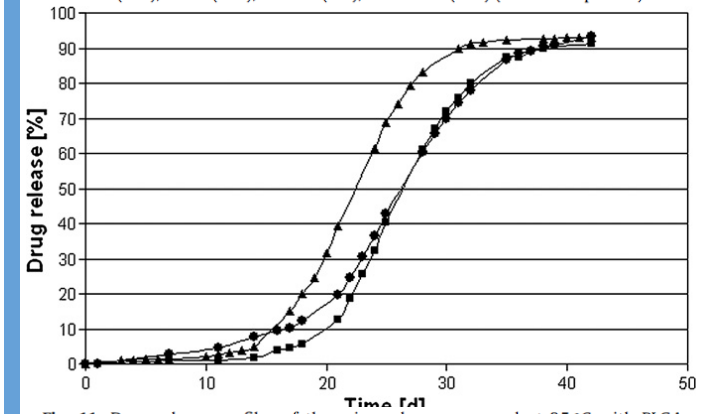


Fig. 11. Drug release profiles of the microspheres prepared at 35 °C with PLGA types of different molecular weights (36,510 Da (-▲-), 58,300 Da (-■-), 109,200 Da (-●-)).

- **In attempt to develop a product with an S-shaped release profile and with a big lag phase, it was found that the higher the manufacturing temperature the better the results. Still not enough though to reach the target (reference product). This finding is not correct for this type of product.**

- **When higher molecular weight polymer was used, the differences after a certain point were very small. Increasing the Mw from 58.3 kDa to 109.2 kDa did not result in more extended release profile, contrary to what was expected.**

Source: Vay et al., A detailed view of microparticle formation by in-process monitoring of the glass transition temperature, European Journal of Pharmaceutics and Biopharmaceutics 81 (2012) 399–408

# The Importance of Case by Case Study

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## Why is not always the PLGA?

- A recent study conducted from the University of Connecticut in collaboration with FDA.

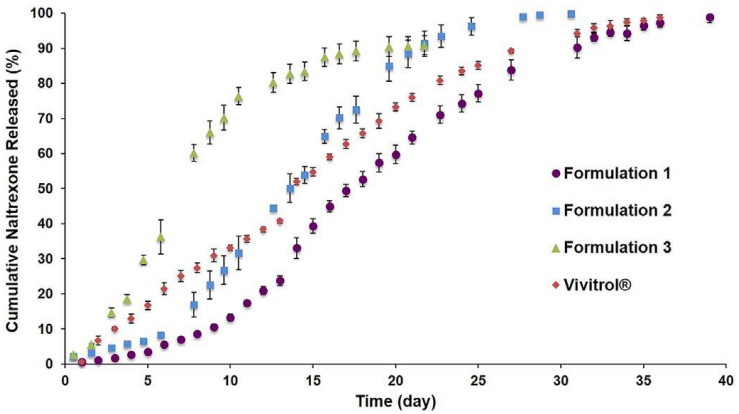
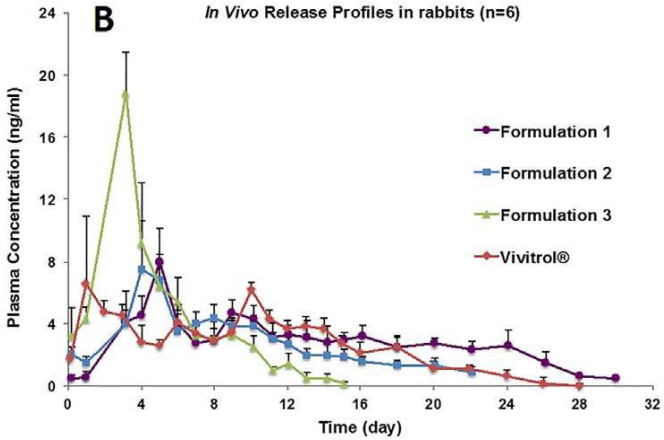



**Fig. 3.** *In vitro* release profiles of compositionally equivalent naltrexone microsphere formulations (with manufacturing differences) and Vivitrol®. The developed USP apparatus 4 method was used at 37 °C in 10 mM PBS (pH 7.4) containing 0.02% (w/v) Tween 20 and 0.02% (w/v) sodium azide ($n$ = 3). The release media was replaced every five days.




intramuscular administration of naltrexone PLGA microspheres at a single dose of 11.69 mg/kg (mean ± SD, $n$ = 6).

- **Again, although the same type of polymer was used (compared to the reference product), the attempts to develop a bioequivalent product have failed.**

- **Contrary to the previous case where different solvent was used, in some of these trials the same type of solvents were used (as in the reference product) in order to manufacture the particles.**

**Table 1**
Physicochemical properties of naltrexone microspheres investigated.

| Sample | Solvent | Preparation method | Drug loading (%, w/w) | Porosity (%, w/w) |
|---|---|---|---|---|
| Formulation 1 | DCM & BA | Magnetic stirring | 28.74 ± 1.64 | 49.83 |
| Formulation 2 | EA & BA | Magnetic stirring | 29.7 ± 1.11 | 58.32 |
| Formulation 3 | EA & BA | Homogenization | 29.57 ± 1.75 | 65.08 |
| Vivitrol® | – | – | 33.50 ± 1.43 | 50.21 |

DCM: methylene chloride, EA: ethyl acetate, BA: benzyl alcohol.

**Porosity in this case is not the critical parameter to explain the differences in the release profile.**

Source: Andhariya et al., Development of in vitro-in vivo correlation of parenteral naltrexone loaded polymeric microspheres, Journal of Controlled Release 255 (2017) 27–35

# The Importance of the Manufact. Process

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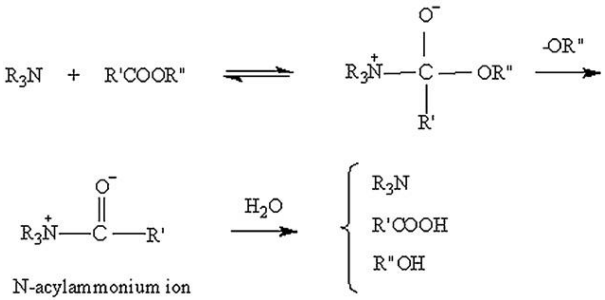
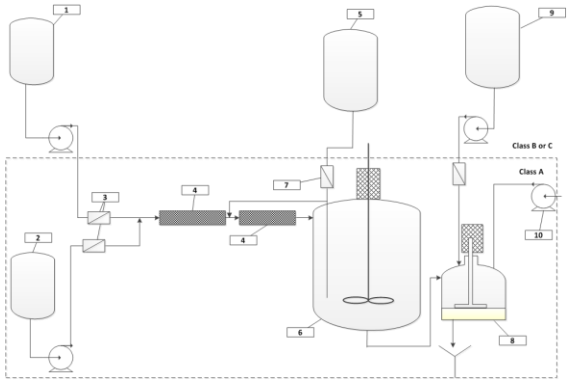
**Q. So If not the PLGA and the solvents – what is missing?**

**A: The difference in the manufacturing process**

- In both previous examples the release profile is not merely govern by the polymer type. In fact the polymer molecular weight, assuming of course that polymer with the same lactide/glycolide ratio is used, has a smaller influence.
- The release profile in both cases is governed by the active ingredient. The reason is the amine catalyzed PLGA hydrolysis caused by the active ingredient (scheme 1).
- Due to this interaction between the drug and the polymer, the most important attributes in achieving the same release profile is the distribution of the drug in the polymer matrix (core loading (S-shaped profile) Vs even distribution of the drug (zero order release)) and the percentage of crystallinity of the drug inside the microparticles.
- All the above attributes related to the drug-polymer interaction, are **merely** controlled by the **manufacturing process**: solvents used (API has different affinity to the different solvents, manufacturing temperature, quenching stirring rate, time and number of drying steps, time and temperature of the washing steps etc.




Scheme 1: Amine catalyzed PLGA hydrolysis via N-acylammonium ion intermediate formation.



Scheme 2: Manufacturing process of PLGA microspheres.

# The Importance of Case by Case Study

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## In hydrophilic drugs where the drug loading is low, PLGA and process dominates the release profile.

- In the case of hydrophilic drugs, where the drug loading is low (around 5%) and the drug does not degrade the polymer, the type of polymer dominates the release characteristics of the drug. As can be seen from the scheme the **linear** and the **star-branched PLGA copolymer** have a totally **different degradation profile**. If it could ever be possibly achieved with linear polymers, it would require a mixture of linear polymers wit different molecular weight.

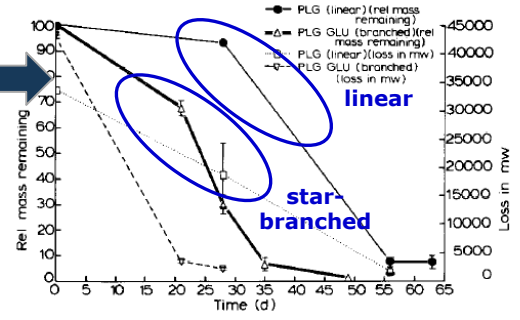
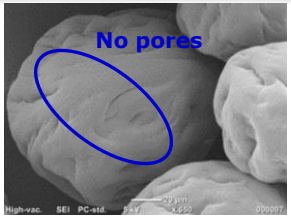



Fig. 8. Biodegradation of PLG-GLU and linear PLG in rats. Mass loss of polymers and molecular weight decay as a function of time.

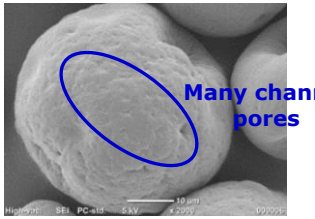
Source: Kissel et al., Parenteral depot-systems on the basis of biodegradable polyesters, Journal of Controlled Release, 16 ( 1991) 27-42

## Do not forget the influence of the manufacturing process

- Also in the case of hydrophilic APIs where the polymer plays the most important role in the release profile, the effect of the manufacturing process crucial. Applying for instance a **double emulsification process** (W/O/W) which is frequently adopted from the generic companies could result to different release profile (even when using the same star-branched polymer) compared to **the coacervation technique** (used by some reference products). The reason is simply because the double emulsification technique results in **more porous particles**. In the coacervation technique (using silicone oil) the inner aqueous phase is trapped and no porous channels are formed through the polymer matrix.



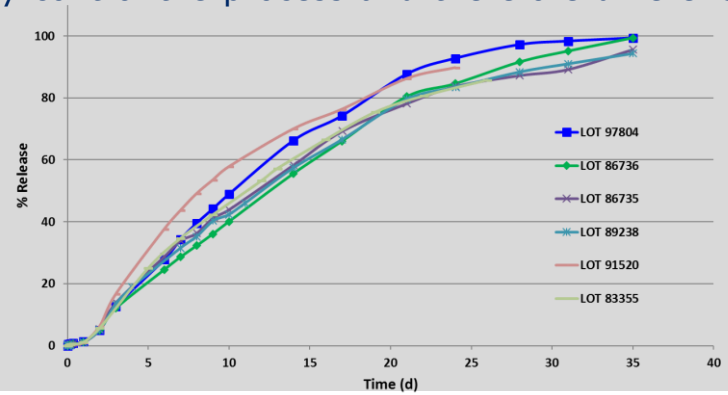

**Particles prepared by the coacervation method**




**Particles prepared by the W/OW method**

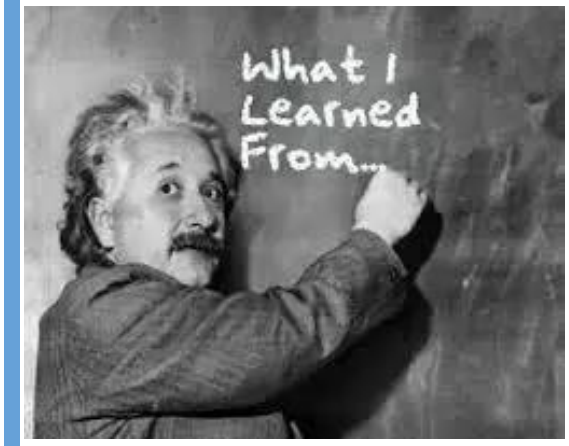
# The Way Forward

- Better understanding of the products, case by case study and provide **hints and guidance through workshops or published data.**
- What is the dominant factor in the release profile in each case?
  - ✓ **type of polymer** (molecular weight, branching, etc.).
  - ✓ **drug distribution and percentage of crystallinity inside the particles.**
- Understanding and controlling the manufacturing process.
  - ✓ **the same manufacturing technique** (solvent extraction and/or evaporation, double emulsification, coacervation etc.).
  - ✓ **applying the same manufacturing steps** (time, temperatures etc.) by controlling the most critical quality attribute in each case (e.g. crystallinity of the API inside particles etc.).
- **IVRT** with In-vivo correlation (IVIVC).
- **Periodic controls** of the reference products.
  - ✓ even the **reference products** sometimes fell short to fully control the process and therefore differences in dissolution profile are observed.



# Conclusions

## The Take Home Message:




- ☑ **Each case in PLGA micropsheres products is different**
- ☑ **In some case (mostly in hydrophilic APIs) the type of polymer dominates the release profile.**
- ☑ **In other cases the impact of the polymer is much smaller and the degradation profile is governed by the encapsulated drug because it causes degradation to the polymer matrix.**
- ☑ **In these cases there are different and more important attributes to be controlled apart from the initial type and molecular weight of the polymer.**
- ☑ **In these cases also, the API/polymer interactions does not affect only the release profile but also the stability of the product (molecular weight, impurities etc.).**
- ☑ **There is definitely the need for a thorough comprehension of the release mechanism in each of the commercial products and the publication of accurate product specific guidelines that take all these critical quality attribures into consideration.**
- ☑ **In all of the products do not forget the importance of the manufacturing process. Slight differences in processing times, temperatures, steps can result in utterly different release profile.**
- ☑ **By mastering the manufacturing processes and the critical quality attributes would lead to one day where less BE studies will be required.**

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