Supplementary information

Methods

Progesterone HPLC Method

The detection and quantification of progesterone using HPLC was performed on an Agilent Infinity 1260 Infinity system with a UV-Vis detector using a method from the literature.[1] The method used reverse-phase chromatography with an Agilent ZORBAX Rapid Resolution High Definition C18 1.8 µm column and an acetonitrile and pH 6.4 phosphate buffer at a flow rate of 1 ml/min. The phosphate buffer solution at pH 6.4 was prepared by dissolving potassium phosphate monobasic monohydrate (4.08 g) was dissolved in purified water (1000 mL) and the final pH was adjusted to 6.4 using 1M potassium hydroxide. The HPLC solvent was using a gradient programme as shown in Table S1 with a total run time of 16 min. An injection volume of 25 µL was used for all samples and detection was carried out at 225 nm. Progesterone samples were prepared using a diluent of acetonitrile and water (70:30 v/v).

Table S1. 1: The gradient programme used for the HPLC analysis of progesterone.

Time	% A Buffer (v/v)	% B Acetonitrile (v/v)	Solvent mode
0.00	75	25	Isocratic
2.00	75	25	Isocratic
12.00	10	90	Gradient
12.01	75	25	Isocratic

Tenofovir Disoproxil Fumarate HPLC Method

The detection and quantification of progesterone using HPLC was performed on an Agilent Infinity 1260 Infinity system with a UV-Vis detector using methods from the literature.[2] The method used reverse-phase chromatography with an Agilent ZORBAX Rapid Resolution High Definition C18 1.8 µm column and an acetonitrile and water (75:25 v/v) at a flow rate of 1 mL/min. An injection volume of 25 µL was used for all samples, the run time was 5 min and the tenofovir disoproxil fumarate detection was carried out at 259 nm. Tenofovir disoproxil fumarate samples were prepared using the same mixture of acetonitrile and water as was used for the mobile phase. Calibrations for tenofovir disoproxil fumarate and progesterone are shown in figure S1.

HPLC Method Validation

The progesterone and tenofovir disoproxil fumarate HPLC methods were validated as laid out by the ICH "Validation of Analytical Procedures" text[3]. The limit of detection, limit of quantification, accuracy and precision were calculated and used to evaluate the HPLC methods. The limit of detection (LOD) and limit of quantification (LOQ) were calculated using Equations S1 and S2 respectively.

$$LOD = \left(\frac{Standard\ Error\ of\ the\ Y\ intercept}{Slope}\right) x\ 3.3 \qquad (Equation\ S1)$$

$$LOQ = \left(\frac{Standard\ Error\ of\ the\ Y\ intercept}{Slope}\right) x\ 10 \qquad (Equation\ S2)$$

The precision of the HPLC methods was evaluated using three concentrations of analyte at low, medium and high concentration. The three concentrations were prepared freshly on three consecutive days and injected 6 times each. The method was deemed precise if the relative standard deviation of the 6 injections was less than or equal to 2 %. The accuracy of the method was evaluated using the same injections as for the method precision. The method percent accuracy was calculated using equation s3, and the method was deemed accurate if the mean percent accuracy was between 98 and 102 % with a relative standard deviation equal or less than 2 %.

$$\%\ Accuracy = \left(\frac{Measured\ Concentration}{Theorectical\ Concentration}\right) x\ 100 \qquad (Equation\ S3)$$

HPLC procedures for progesterone and tenofovir disoproxil fumarate satisfied the above conditions and were considered to be "validated".

Calculation of solubilising power, micelle:water partition coefficient and critical micelle concentrations (CMCs)

The CMC was determined from the progesterone solubilisation data (figure 8) using equation S4, where the "region of increased solubility" was fitted to a straight line and the "flat line" refers to the region where drug solubility did not increase with polymer concentration. The CMC could then be used to calculate the solubilising power at 10 mg/mL polymer

concentration (equation S5). The data in figure 8 was also used to calculate the micelle:water partition coefficient (equation S6).

$$CMC = \left(\frac{Intercept\ of\ Region\ of\ Increased\ Solubility - Intercept\ of\ th}{Slope\ of\ Region\ of\ Increased\ Solubility - Slope\ of\ the\ Fl}\right.$$

$$solubilising\ power = \left(\frac{Cd - Cw}{Cp - CMC}\right) \qquad (Equation\ S5)$$

$$micelle{:}water\ partition\ coefficient\ = \left(\frac{Cd - Cw}{Cw}\right) \qquad (Equation\ S6)$$

Where Cd is the concentration of drug dissolved at a given polymer concentration (Cp). Cw is the saturation concentration of drug in water. Calculations were performed on a mg/mL basis.

Results

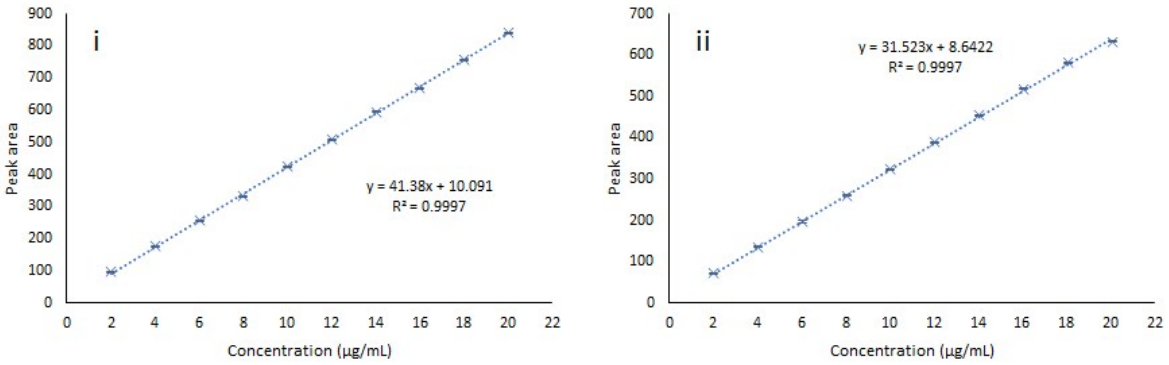

Figure S1. Calibration curves for progesterone (i) and tenofovir disoproxil fumarate (ii). Data present as mean ± standard deviation, n= 3

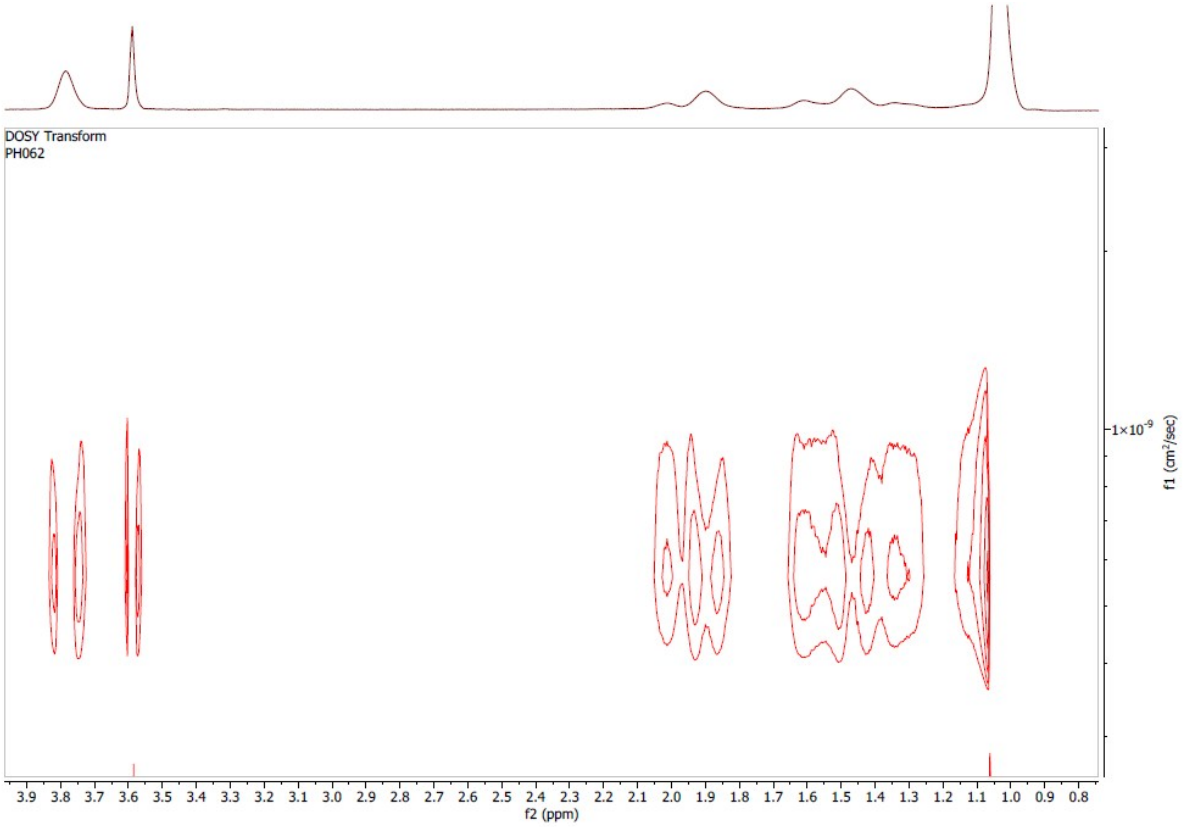

Figure S2: DOSY NMR of $PNIPAM_{98}$-PEG_{122}-$PNIPAM_{98}$

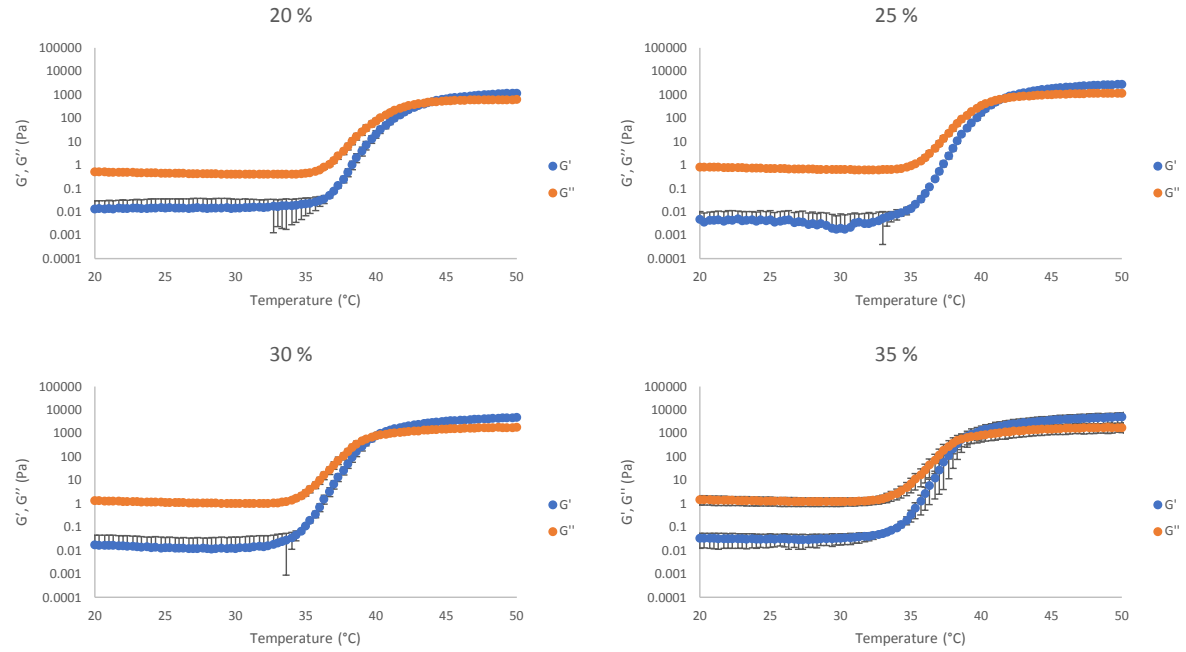

Figure S3. Additional rheological temperature ramps for $PNIPAM_{98}$-PEG_{122}-$PNIPAM_{98}$ used to determine rheological parameters in figure 3. Data present as mean ± standard deviation, n= 3

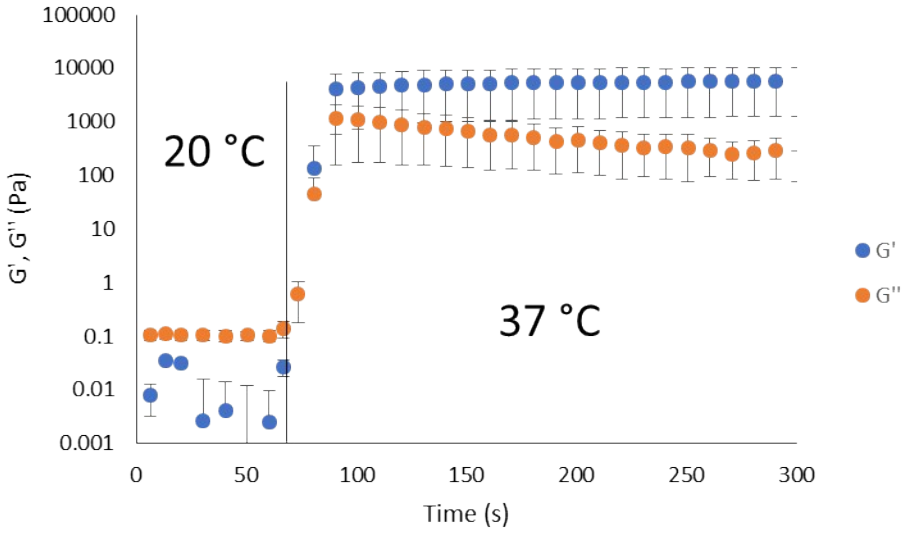

Figure S4. Time-dependence of 20 % (w/v) poloxamer 407 gelation determined by rheometry. Data present as mean ± standard deviation, n= 3

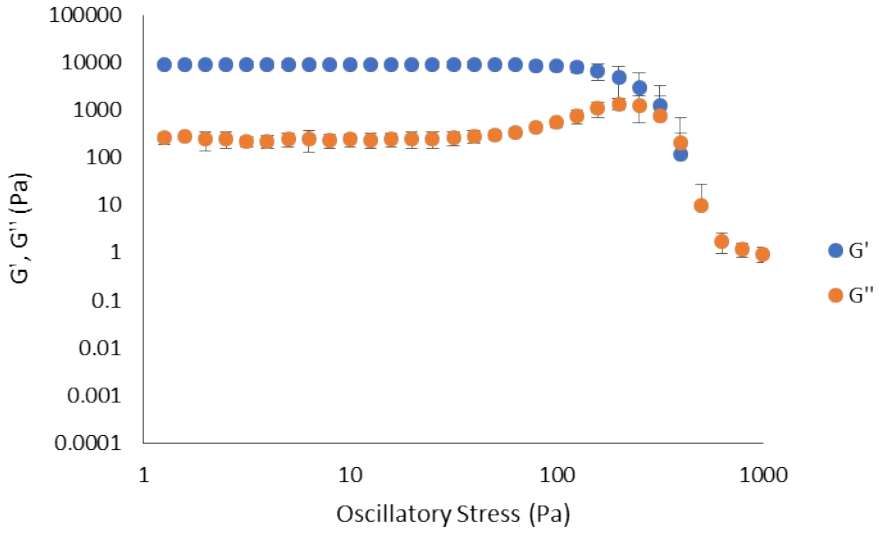

Figure S5. Oscillatory stress sweep of 20 % (w/v) poloxamer 407 at 37 °C. Data present as mean ± standard deviation, n= 3

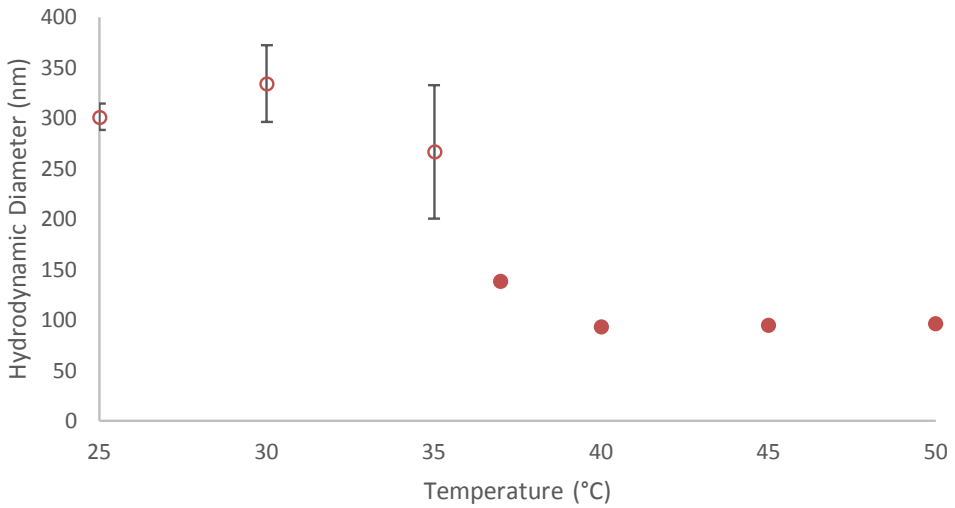

Figure S6. Effect of temperature on the hydrodynamic diameter of $PNIPAM_{98}$-PEG_{122}-$PNIPAM_{98}$ (10 mg/mL). Please note that the open circles designate a point of low count rate (< 12 kcps) which was taken as an indicator that no particles were present.

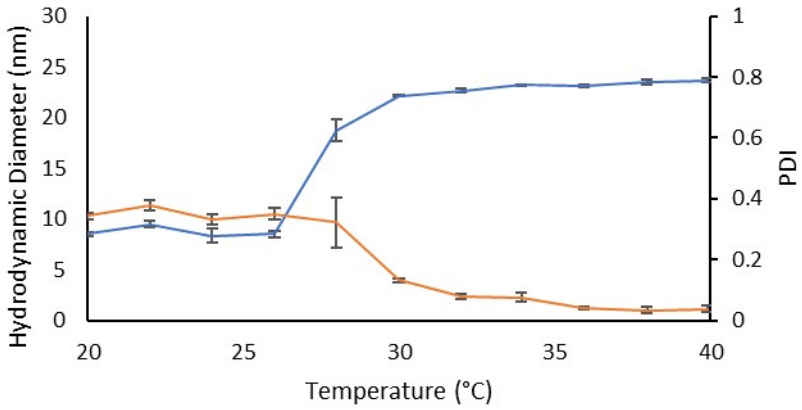

Figure S7. Effect of temperature on the hydrodynamic diameter (blue) and PDI (orange) of 10 mg/mL poloxamer 407 saturated with progesterone for 24 h and filtered (0.4 µm) prior to analysis. Data present as mean ± standard deviation, n= 3

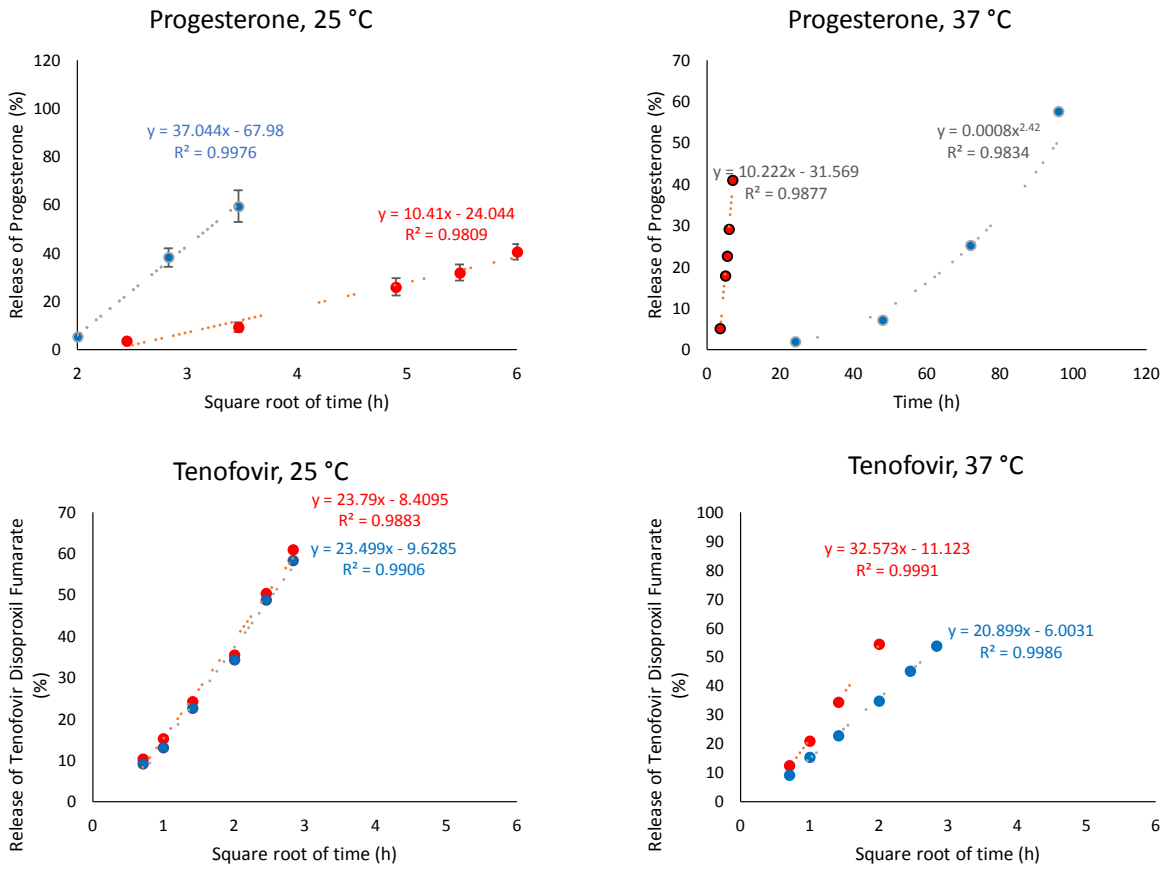

Figure S8. Fitting of drug release kinetics for $PNIPAM_{98}$-PEG_{122}-$PNIPAM_{98}$ (blue) and poloxamer 407 (red). Equations and fit shown inlaid in blue for $PNIPAM_{98}$-PEG_{122}-$PNIPAM_{98}$ and red for poloxamer 407.

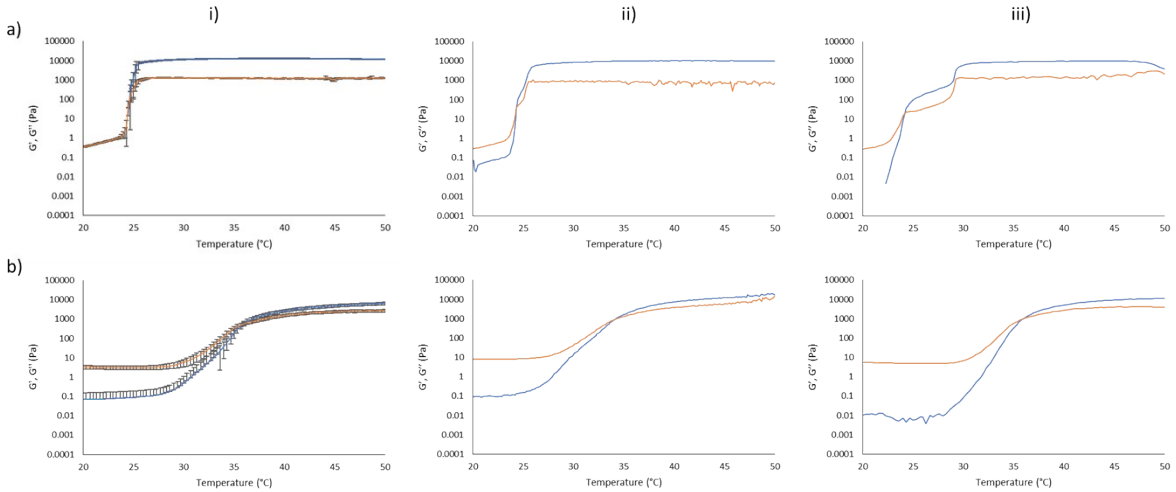

Figure S9. Temperature ramp rheology profiles showing the change in G’ (blue) and G’’ (orange) for poloxamer 407 (20 %) (a) and PNIPAM10-PEG10-PNIPAM10 (50 %) in aqueous solution (i), and in the presence of 50 µg/mL progesterone (n=1) (ii) and with 50 µg/mL tenofovir disoproxil fumarate (n=1) (iii).

1 P. Gautam and T. Purvis, *Pharm. Anal. Chem.*, 2017, **03**, 1.

2 P. B. Kandagal, D. H. Manjunatha, J. Seetharamappa and S. S. Kalanur, *Anal. Lett.*, 2008, **41**, 561–570.

3 *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)*, 2005, **1994**, 17.