APPENDIX A

CASE STUDIES: POST MARKETING SAFETY REPORTING (PMSR) FOR COMBINATION PRODUCTS

Case Study #1: Prefilled Syringe for Approved Biologic / Drug

PharmCo has been marketing "Wonder1," a biological product in a prefilled syringe S1 presentation for treatment of rheumatoid arthritis (RA) that would deliver a 1.0 mL SC dose. The syringes S1 are manufactured by SyringeCo, who also separately markets empty syringes. The finished product is filled, packaged and sterilized by PharmCo. This product is a combination product.

- The label includes reports of severe allergic reaction including anaphylaxis, injection site reaction, pain etc.
- Since product launch ICSRs have been filed to CBER.
- Adverse Events (AEs) and Product Quality (PQC) / Device complaints (DC) are stored in 2 separate databases

For each individual scenario below review and discuss if a PMSR Report needs to be filed? Provide details including PMSR report type(s), submitted to branch, report due dates, responsible organization and team rationale for the decision. Unless specified consider each event as standalone events.

September 2019 PharmCo receives:

A) *1-Sep-2019 - Report of an anaphylactic reaction immediately post injection in a new patient.*
B) *1-Sep-2019 - Report of a rare tumor in a patient taking 'Wonder1" for 5 years.*
C) *1-Sep-2019 - Report of premature deployment of needle leading to accidental needle stick.*
D) *1-Sep-2019 – Report of breakage and embedded fragments of the subcutaneous needle, leading to surgical intervention (incision and removal)*
E) *For event C) on 7-Sep-2019 – SyringeCo separately informs PharmCo that they have confirmed malfunctiosn of their needle protection mechanism leading to premature deployment of needle. They have confirmed and reported to FDA multiple events.*
F) *For event C) on 14-Sep-2019 - SyringeCo informs PharmCo that they are conducting a field correction to inform users to take extra caution and recommend safe use and disposal of S1.*
G) *Multiple reports of anaphylactic reactions were reported leading to an investigation of the trend. The investigation confirmed potential contamination of Wonder 1 during manufacturing process.*
H) *PharmCo observed in-house out-of-box a needle misfire with force (potential to cause injury to eye), there have been no complaints or injuries reported.*
I) *Review reports A-H above which of these reports need to be included as Combination Product ICSR Information in Periodic Safety Reports?*
J) *PharmCo is the US MAH for BLA-led Combination Product "Wonder1,". PharmCo also markets another Combination Product OUS, "Super1," that has the same device constituent "S1," prefilled with a different drug (with a different risk profile). "Super1" is not marketed in the*

US. PharmCo receives an OUS report on "Super1", that the tip of syringe "S1" broke off during injection, resulting in the needle detaching and remaining in the patient's arm There are no similar events reported for "Wonder1".

K) *PharmCo is studying (Clinical trials) a different dose and concentration of Wonder1 as "Wonder2" for a new indication with a high-risk profile. A needle block occurs causing under-delivery of the drug leading to a hospitalization.*

Case Study #2: Drug Eluting Stent

StentCo markets "Stentastic1." It consists of drug "Supermed" coated "stent1" for treatment of Coronary Artery Disease. The Stent1 is manufactured by StentCo but "Supermed" is sourced from DrugCo. The finished combination product is manufactured, packaged and sterilized by StentCo.

- The IFU includes reports of death, stroke, cardiac arrest as observed in clinical trials etc.
- Since product launch MDRs have been filed to CDRH.
- Adverse Events (AEs) and Product Quality (PQC) / Device complaints (DC) are all stored in a single database

For each individual scenario below review and discuss if a PMSR Report needs to be filed? Provide details including PMSR report type(s), submitted to branch, report due dates, responsible organization and team rationale for the decision. Unless specified consider each event as standalone events.

September 2019 StentCo receives:

A) *1-Sep-2019 - Report of a stroke immediately post implant in a patient.*

B) *1-Sep-2019 - Report of a drug reaction in a patient 5 years after implant of "Stentastic1". These reactions have been observed and labeled in the "Supermed" drug label*

C) *1-Sep-2019 - Report of a rare tumor in a patient 5 years after implant of "Stentastic1". These tumors have not been observed or labeled in the "Supermed" drug label. Physician alleges these are related to the "Supermed"*

D) *1-Sep-2019 - Report of premature deployment of "Stentastic1" out-of-box was observed with no report of harm or injury.*

E) *For event C) on 7-Sep-2019 – DrugCo informs StentCo that they have confirmed drug class effect and updated their product label to include these tumors. They have confirmed and reported to FDA multiple similar events.*

F) *For event B) on 14-Sep-2019 - DrugCo informs StentCo that they are conducting a field correction for lots 123 and 456 of the "Supermed" to inform users about a quality issue related to these lots causing a higher potency of drug than expected.*

G) *Multiple reports of stent fractures were reported leading to an investigation of the trend. The investigation confirmed potential quality issue with raw materials used for 2 lots (123, 456) of stents during manufacturing process.*

H) *StentCo is the US Manufacturer for "Stentastic1" but also markets another Combination Product OUS, "Stentastic2" that has the same device constituent "S1," coated with a different drug (with a different risk profile). "Stentastic2" is not marketed in the US. StentCo receives an OUS report on, "Stentastic2" that the stent "S1" prematurely dislodged during deployment, resulting in the need to use a surgical snare to remove the stent and deploy another stent causing a delay in the procedure (Serious Injury). There are no similar events reported for "Stentastic1".*

I) *StentCo is studying (Clinical trials) a different dose and concentration of "Supermed" as "Superdupermed" for a new indication with a high-risk profile. An increase in stent fractures is observed during the trial.*

Case Study #3: Constituent Part Manufacturer

LaserCo holds the approved PMA for the laser system (device) "Superlaser" and LitDrugCo holds the approved NDA for the light-activated drug "Liteup1". Together they comprise a cross-labeled combination product, making each sponsor a "Constituent Part Applicant" under the combination product PMSR Rule.

> For each individual scenario below review and discuss if a PMSR Report needs to be filed? Provide details including PMSR report type(s), submitted to branch, report due dates, responsible organization and team rationale for the decision. Unless specified consider each event as standalone events. Consider Information sharing requirements in your responses.

September 2019:

A) *1-Sep-2019 - LaserCo receives a report of an anaphylactic reaction during the laser procedure immediately after administration of LiteUp1 in a patient. The laser was not used.*

B) *1-Sep-2019 – LitDrugCo receives a report of an unintended fetal exposure to "Superlaser"*

C) *1-Sep-2019 – During investigation of a complaint of a humming noise in the device "Superlaser", LaserCo identified a quality defect in the unit that may lead to an overheating of the laser with a potential to cause 3rd degree burns. There have been no reports of harm or injury.*

D) *For event C) on 7-Sep-2019 – LaserCo has confirmed a product deficiency in certain lots of "Superlaser". They have received multiple similar events.*

E) *For event C) on 14-Sep-2019 – LaserCo is conducting a field correction for certain impacted lots of "Superlaser".*

F) *LitDrugCo received a report of discoloration of the product LiteUp1 and leakage from the container.*

Final: Discuss key takeaways and challenges

Case Study Worksheets # ____

Organization Responsible for Reporting:

Report due date in the relevant column:
FDA Branch to Submit:

	Case Studies	15-day 15 c-days	Malfunction Report 30 c-days	5-day 3 w-days	Correction/ Removal 10 w-days	Periodic Report	FAR 3 w-days	BPDR 45 c-days	Rationale
	A								
	B								
	C								
	D								
	E								
	F								