

## CDER Breakthrough Therapy Designation Approvals

As of December 31, 2016

| Application Number | Submission Type and Number | Proprietary Name | Established Name | Applicant                            | Approval Date | Use  |
|--------------------|----------------------------|------------------|------------------|--------------------------------------|---------------|--|
| NDA 209115         | ORIGINAL-1                 | RUBRACA          | RUCAPARIB        | CLOVIS ONCOLOGY INC                  | 19-Dec-2016   | Treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA   |
| BLA 761036         | SUPPLEMENT-3               | DARZALEX         | DARATUMUMAB      | JANSSEN BIOTECH INC                  | 21-Nov-2016   | Treatment of patients with multiple myeloma who have received at least one prior therapy, in combination with lenalidomide and dexamethasone   |
| BLA 761036         | SUPPLEMENT-4               | DARZALEX         | DARATUMUMAB      | JANSSEN BIOTECH INC                  | 21-Nov-2016   | Treatment of patients with multiple myeloma who have received at least one prior therapy, combination with bortezomib and dexamethasone  |
| BLA 125554         | SUPPLEMENT-22              | OPDIVO           | NIVOLUMAB        | BRISTOL-MYERS SQUIBB COMPANY         | 10-Nov-2016   | Treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after platinum-based therapy   |
| BLA 125514         | SUPPLEMENT-8               | KEYTRUDA         | PEMBROLIZUMAB    | MERCK SHARP & DOHME CORP             | 24-Oct-2016   | Treatment of patients with metastatic NSCLC whose tumors express PD-L1 [Tumor Proportion Score (TPS) > 1%] as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy   |
| BLA 761038         | ORIGINAL-1                 | LARTRUVO         | OLARATUMAB       | ELI LILLY AND COMPANY                | 19-Oct-2016   | Treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype, in combination with doxorubicin, for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery |
| BLA 761041         | ORIGINAL-1                 | TECENTRIQ        | ATEZOLIZUMAB     | GENENTECH INC                        | 18-Oct-2016   | Treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy   |
| BLA 125319         | SUPPLEMENT-85              | ILARIS           | CANAKINUMAB      | NOVARTIS PHARMACEUTICALS CORPORATION | 28-Sep-2016   | Treatment of Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)   |

|            |               |           |                               |   |             |  |
|------------|---------------|-----------|-------------------------------|---|-------------|--|
| BLA 125319 | SUPPLEMENT-86 | ILARIS    | CANAKINUMAB                   | NOVARTIS<br>PHARMACEUTICALS<br>CORPORTATION | 28-Sep-2016 | Treatment of Hyperimmunoglobulin D<br>Syndrome (HIDS)  |
| BLA 125319 | SUPPLEMENT-87 | ILARIS    | CANAKINUMAB                   | NOVARTIS<br>PHARMACEUTICALS<br>CORPORTATION | 28-Sep-2016 | Treatment of Familial Mediterranean Fever<br>(FMF)   |
| NDA 206038 | SUPPLEMENT-5  | ORKAMBI   | LUMACAFITOR and<br>IVACAFITOR | VERTEX PHARMACEUTICALS<br>INC               | 28-Sep-2016 | Treatment of cystic fibrosis patients who are<br>homozygous for the F508del mutation in the<br>CFTR gene, ages 6-11  |
| NDA 208341 | ORIGINAL-1    | EPCLUSA   | SOFOSBUVIR and<br>VELPATASVIR | GILEAD SCIENCES INC                         | 28-Jun-2016 | Treatment of adult patients with chronic<br>hepatitis C virus (HCV) genotypes 1, 2, 3, 4,<br>5 or 6 infection: - without cirrhosis or with<br>compensated cirrhosis - with<br>decompensated cirrhosis for use in<br>combination with ribavirin   |
| BLA 761034 | ORIGINAL-1    | TECENTRIQ | ATEZOLIZUMAB                  | GENENTECH INC                               | 18-May-2016 | Treatment of locally advanced or metastatic<br>urothelial carcinoma who have disease<br>progression during or following platinum-<br>containing chemotherapy or have disease<br>progression within 12 months of neoadjuvant<br>or adjuvant treatment with platinum-<br>containing chemotherapy |
| BLA 125554 | SUPPLEMENT-19 | OPDIVO    | NIVOLUMAB                     | BRISTOL-MYERS SQUIBB<br>COMPANY             | 17-May-2016 | Treatment of Hodgkin Lymphoma  |
| NDA 206947 | SUPPLEMENT-3  | LENVIMA   | LENVATINIB<br>MESYLATEL       | EISAI INC                                   | 13-May-2016 | Treatment of renal cell cancer (RCC): in<br>combination with everolimus, for patients with<br>advanced RCC following one prior anti-<br>angiogenic therapy   |
| NDA 207318 | ORIGINAL-1    | NUPLAZID  | PIMAVANSERIN                  | ACADIA PHARMACEUTICALS<br>INC               | 29-Apr-2016 | Treatment of hallucinations and delusions<br>associated with Parkinson's disease<br>psychosis  |
| NDA 208692 | ORIGINAL-1    | CABOTETYX | CABOZANTINIB                  | EXELIXIS INC                                | 25-Apr-2016 | Treatment of patients with advanced renal<br>cell carcinoma (RCC) who have received<br>prior anti-angiogenic therapy   |
| NDA 208573 | ORIGINAL-1    | VENCLEXTA | VENETOCLAX                    | ABBVIE INC                                  | 11-Apr-2016 | Treatment of patients with chronic<br>lymphocytic leukemia (CLL) with 17p deletion<br>who have received at least one prior therapy   |
| NDA 202570 | SUPPLEMENT-16 | XALKORI   | CRIZOTINIB                    | PF PRISM CV                                 | 11-Mar-2016 | Treatment of patients with non- small cell<br>lung cancer whose tumors are ROS-1<br>positive   |

|            |               |           |                          |  |             |   |
|------------|---------------|-----------|--------------------------|--|-------------|---|
| NDA 207103 | SUPPLEMENT-2  | IBRANCE   | PALBOCICLIB              | PFIZER INC                               | 19-Feb-2016 | Treatment hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy           |
| NDA 208261 | ORIGINAL-1    | ZEPATIER  | GRAZOPREVIR and ELBASVIR | MERCK SHARP AND DOHME CORP               | 28-Jan-2016 | Treatment of chronic hepatitis C virus (HCV) genotypes 1 and 4 infections in adults   |
| BLA 125514 | SUPPLEMENT-6  | KEYTRUDA  | PEMBROLIZUMAB            | MERCK SHARP & DOHME CORP                 | 18-Dec-2015 | Treatment of patients with unresectable or metastatic melanoma  |
| NDA 208434 | ORIGINAL-1    | ALECENSA  | ALECTINIB                | HOFFMANN-LA ROCHE INC                    | 11-Dec-2015 | Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC), who have progressed on or are intolerant to crizotinib  |
| BLA 125561 | ORIGINAL-1    | KANUMA    | SEBELIPASE ALFA          | SYNAGEVA BIOPHARMA CORP                  | 08-Dec-2015 | Treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency  |
| BLA 761035 | ORIGINAL-1    | EMPLICITI | ELOTUZUMAB               | BRISTOL-MYERS SQUIBB COMPANY             | 30-Nov-2015 | Treatment of patients with multiple myeloma who have received one to three prior therapies  |
| BLA 125554 | SUPPLEMENT-12 | OPDIVO    | NIVOLUMAB                | BRISTOL-MYERS SQUIBB COMPANY             | 23-Nov-2015 | Treatment of advanced renal cell carcinoma patients who have received prior antiangiogenic therapy  |
| BLA 761036 | ORIGINAL-1    | DARZALEX  | DARATUMUMAB              | JANSSEN BIOTECH INC                      | 16-Nov-2015 | Treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent |
| NDA 208065 | ORIGINAL-1    | TAGRISSEO | OSIMERTINIB              | ASTRAZENECA PHARMACEUTICALS LP           | 13-Nov-2015 | Treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA approved test, who have progressed on or after EGFR TKI therapy                 |
| BLA 125513 | ORIGINAL-1    | STRENSIQ  | ASFOTASE ALFA            | ALEXION PHARMACEUTICALS INC              | 23-Oct-2015 | Treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)   |
| BLA 761025 | ORIGINAL-1    | PRAXBIND  | IDARUCIZUMAB             | BOEHRINGER INGELHEIM PHARMACEUTICALS INC | 16-Oct-2015 | Treatment of patients treated with Pradaxa® when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding   |

|            |                |           |                                     |                               |             |   |
|------------|----------------|-----------|-------------------------------------|-------------------------------|-------------|---|
| BLA 125554 | SUPPLEMENT-5   | OPDIVO    | NIVOLUMAB                           | BRISTOL-MYERS SQUIBB COMPANY  | 09-Oct-2015 | Treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO |
| BLA 125514 | SUPPLEMENT-5   | KEYTRUDA  | PEMBROLIZUMAB                       | MERCK SHARP & DOHME CORP      | 02-Oct-2015 | Treatment of patients with metastatic, PD-L1 positive, non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy   |
| NDA 208169 | ORIGINAL-1     | XURIDEN   | URIDINE TRIACETATE                  | WELLSTAT THERAPEUTICS CORP    | 04-Sep-2015 | Treatment of hereditary orotic aciduria   |
| NDA 207931 | ORIGINAL-1     | TECHNIVIE | OMBITASVIR, PARITAPREVIR, RITONAVIR | ABBVIE INC                    | 24-Jul-2015 | Treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis   |
| NDA 206038 | ORIGINAL-1     | ORKAMBI   | LUMACAFTOR/IVA CAFTOR               | VERTEX PHARMACEUTICALS INC    | 02-Jul-2015 | Treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene   |
| NDA 21110  | SUPPLEMENT-73  | RAPAMUNE  | SIROLIMUS                           | PF PRISM CV                   | 28-May-2015 | Treatment of patients with lymphangioleiomyomatosis (LAM)   |
| NDA 21083  | SUPPLEMENT-55  | RAPAMUNE  | SIROLIMUS                           | PF PRISM CV                   | 28-May-2015 | Treatment of patients with lymphangioleiomyomatosis (LAM)   |
| BLA 125387 | SUPPLEMENT-48  | EYLEA     | AFLIBERCEPT                         | REGENERON PHARMACEUTICALS INC | 25-Mar-2015 | Treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME)  |
| NDA 207925 | ORIGINAL-1     | KALYDECO  | IVACAFTOR                           | VERTEX PHARMACEUTICALS INC    | 17-Mar-2015 | Treatment of cystic fibrosis patients 2 years and older who have one of the following mutations in CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H  |
| BLA 125156 | SUPPLEMENT-106 | LUCENTIS  | RANIBIZUMAB                         | GENENTECH INC                 | 06-Feb-2015 | Treatment of Diabetic Retinopathy (DR) in patients with Diabetic Macula Edema (DME)   |
| NDA 207103 | ORIGINAL-1     | IBRANCE   | PALBOCICLIB                         | PFIZER INC                    | 03-Feb-2015 | Treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease   |
| NDA 205552 | SUPPLEMENT-2   | IMBRUVICA | IBRUTINIB                           | PHARMACYCLICS LLC             | 29-Jan-2015 | Treatment of patients with Waldenström's macroglobulinemia  |

|            |               |             |   |   |             |   |
|------------|---------------|-------------|---|---|-------------|---|
| NDA 203188 | SUPPLEMENT-14 | KALYDECO    | IVACAFTOR                                 | VERTEX<br>PHARMACEUTICALS INC               | 29-Dec-2014 | Treatment of cystic fibrosis in patients age 6 years and older who have the R117H mutation in the CF transmembrane conductance regulator (CFTR) gene  |
| BLA 125554 | ORIGINAL-1    | OPDIVO      | NIVOLUMAB                                 | BRISTOL-MYERS SQUIBB<br>COMPANY             | 22-Dec-2014 | Treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor   |
| NDA 206619 | ORIGINAL-1    | VIEKIRA PAK | OMBITASVIR,<br>PARITAPREVIR,<br>RITONAVIR | ABBVIE INC                                  | 19-Dec-2014 | Treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis  |
| BLA 125557 | ORIGINAL-1    | BLINCYTO    | BLINTUMOMAB                               | AMGEN IINC                                  | 03-Dec-2014 | Treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)  |
| NDA 22535  | ORIGINAL-1    | ESBRIET     | PIRFENIDONE                               | GENENTECH INC                               | 15-Oct-2014 | Treatment of idiopathic pulmonary fibrosis (IPF)  |
| NDA 205832 | ORIGINAL-1    | OFEV        | NINTEDANIB                                | BOEHRINGER INGELHEIM<br>PHARMACEUTICALS INC | 15-Oct-2014 | Treatment of idiopathic pulmonary fibrosis (IPF)  |
| NDA 205834 | ORIGINAL-1    | HARVONI     | SOFOBUVIR/LEDI<br>PASVIR                  | GILEAD SCIENCES INC                         | 10-Oct-2014 | Treatment of chronic hepatitis C, genotype 1 infection  |
| BLA 125514 | ORIGINAL-1    | KEYTRUDA    | PEMBROLIZUMAB                             | MERCK SHARP & DOHME<br>CORP                 | 04-Sep-2014 | Treatment of patients with unresectable or metastatic melanoma & disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor                                   |
| NDA 22291  | SUPPLEMENT-12 | PROMACTA    | ELTROMBOPAG                               | GLAXOSMITHKLINE                             | 26-Aug-2014 | Treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy  |
| NDA 205552 | SUPPLEMENT-1  | IMBRUVICA   | IBRUTINIB                                 | PHARMACYCLICS INC                           | 28-Jul-2014 | Treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and CLL with 17p deletion  |
| NDA 206545 | ORIGINAL-1    | ZYDELIG     | IDELALISIB                                | GILEAD SCIENCES INC                         | 23-Jul-2014 | Treatment of relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities |
| NDA 205755 | ORIGINAL-1    | ZYKADIA     | CERITINIB                                 | NOVARTIS<br>PHARMACEUTICALS CORP            | 29-Apr-2014 | Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib                         |

|            |               |           |              |  |             |   |
|------------|---------------|-----------|--------------|--|-------------|---|
| BLA 125326 | SUPPLEMENT-60 | ARZERRA   | OFATUMUMAB   | GLAXO GROUP LIMITED<br>D/B/A GLAXOSMITHKLINE | 17-Apr-2014 | Treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate |
| NDA 203188 | SUPPLEMENT-4  | KALYDECO  | IVACAFTOR    | VERTEX<br>PHARMACEUTICALS INC                | 21-Feb-2014 | Treatment of cystic fibrosis patients age 6 years and older who have mutations in the CFTR gene   |
| NDA 204671 | ORIGINAL-1    | SOVALDI   | SOFOSBUVIR   | GILEAD SCIENCES INC                          | 06-Dec-2013 | Treatment of chronic hepatitis C infection  |
| NDA 205552 | ORIGINAL-1    | IMBRUVICA | IBRUTINIB    | PHARMACYCLICS INC                            | 13-Nov-2013 | Treatment of patients with mantle cell lymphoma (MCL)   |
| BLA 125486 | ORIGINAL-1    | GAZYVA    | OBINUTUZUMAB | GENENTECH INC                                | 01-Nov-2013 | Treatment of patients with previously untreated chronic lymphocytic leukemia in combination with chlorambucil                                     |

\* Breakthrough Therapy designation was enacted in the Food and Drug Administration Safety and Innovation Act on July 9, 2012. There were no approvals in CY 2012.