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EDITED TRANSCRIPT

PFE.N - Q2 2021 Pfizer Inc Earnings Call

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OVERVIEW:

PFE reported that 2Q21 revenue increased 86% YoverY operationally. Co. expects 2021 revenue to be $78-80b and adjusted diluted EPS to be $3.95-4.05.

REFINITIV

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PRESENTATION

Operator

Good day, everyone, and welcome to Pfizer's Second Quarter 2021 Earnings Conference Call. Today's call is being recorded. At this time, I would like to turn the call over to Mr. Chris Stevo, Senior Vice President and Chief [Investor] (corrected by the company after the call) Relations Officer. Please go ahead, sir.

Christopher J. Stevo - *Pfizer Inc. - Senior VP & Chief IR Officer*

Thank you, Sylvia. Good morning. It's my pleasure to be welcoming you to Pfizer's second quarter earnings call for the first time as the Head of Investor Relations at Pfizer. I'm joined today by Dr. Albert Bourla, our Chairman and CEO; Frank D'Amelio, our CFO; Mikael Dolsten, President of Worldwide Research and Development and Medical; Angela Hwang, Group President, Pfizer Biopharmaceuticals Group; John Young, our Chief Business Officer; and Doug Lankler, General Counsel.

We'll begin the call with remarks by Albert, followed by a pipeline update from Mikael, and Frank will then give you his thoughts on the numbers and our updated guidance before we open up the call for Q&A. Finally, Albert will come back for concluding comments. We expect this call to last 90 minutes.

The materials for this call as well as all the other earnings-related materials have been posted to the Investor Relations section of pfizer.com.

As you can see on Slide 3, we will be making forward-looking statements during the call regarding, amongst other topics, our anticipated future operating and financial performance, business plans and prospects, and expectations for our product pipeline and marketed products, which are subject to risks and uncertainties as well as the use of non-GAAP financial information.

Additional information regarding forward-looking statements and our non-GAAP financial measures is available in our earnings release including under the Disclosure Notice section and under Risk Factors in our SEC Forms 10-K and 10-Q. Forward-looking statements on the call speak only as of the call's original date, and we undertake no obligation to update or revise any of the statements.

With that, I will turn over the call to Dr. Bourla. Albert, please go ahead.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Chris, and I think there was a problem with your line at the last sentence, so you can have a look on that. Welcome to your first Pfizer earnings call as our new Chief Investor Relations Officer.

Hello, everyone. I'm proud to say that Pfizer delivered an outstanding second quarter. Most notably, we delivered extremely strong financial results, even excluding direct lines -- even excluding direct sales and alliance revenue provided by our COVID-19 vaccine. We generated 10% operational revenue growth compared to the prior year quarter. And I would note that the year ago quarter was also very strong, delivering 6% operational growth for the comparable business.

At the same time, we continued to accelerate the production and delivery of the Pfizer-BioNTech COVID-19 vaccine. And in collaboration with BioNTech, we have now shipped more than 1 billion doses since last December. This is truly remarkable, especially when you consider that prior to the pandemic, Pfizer produced approximately 200 million doses annually across our entire vaccines portfolio.

Let me start with the commentary on some of our biggest growth drivers in the quarter. The Pfizer-BioNTech COVID-19 vaccine contributed $7.8 billion in global revenues during the second quarter, and we continue to sign agreements with governments around the world. Just last week, we announced that the U.S. government has purchased an additional 200 million doses of the vaccine, bringing the total number of doses to be supplied to the U.S. government under its existing supply agreement to 500 million. This is in addition to the 500 million doses that we agreed to provide to the U.S. government at a not-for-profit price to be donated to the poorest countries in the world.

We anticipate that the significant amount of the remaining 2021 vaccine manufacturing capacity will be delivered to middle- and low-income countries where we price in line with income levels or at a not-for-profit price. In fact, we are on track to deliver on our commitment to provide this year more than 1 billion doses or approximately 40% of our total production to middle- and low-income counties and another 1 billion in 2022.

Vyndaqel and Vyndamax revenues were up 77% operationally to $501 million globally. Our disease educational efforts in the U.S. continue to support increases in appropriate diagnosis, while the main driver of growth in Japan has been the successful establishment of several referral networks in select areas, resulting in new patient starts. We anticipate these efforts will continue to support a strong trajectory for the franchise.

Eliquis continued its strong performance, with revenues up 13% operationally to $1.5 billion. This was led by growth in the U.S. and emerging markets, driven primarily by strength of the clinical profile, ease of use for both patients and clinicians, continued increased adoption in nonvalvular atrial fibrillation and overall oral anticoagulant market share gains.

Prevnar 13 in the U.S. was up 34% overall to $642 million. This growth was due primarily to higher levels of health care activity and wellness visits compared with the prior year quarter, which was heavily impacted by COVID-19-related mobility restrictions and limitations. Growth in the pediatric indication was also due to year-over-year government purchasing patterns and was partially offset by lower year-over-year birth rates.

Growth in the adult indication was partially offset by the continued impact of the lower remaining eligible unvaccinated population. During the quarter, the U.S. Food and Drug Administration approved Prevnar 20 for adult ages 18 and over for the prevention of both invasive disease and

pneumonia caused by the 20 pneumococcal serotypes in the vaccine. I would note that a 15-valent vaccine also recently received FDA approval in adults. However, that approval did not include the pneumonia indication.

We believe the only way to add that indication to the 15-valent vaccine in the U.S. will be to conduct a post-licensure efficacy -- effectiveness trial, which we believe means that for the foreseeable future, Prevnar 20 likely will be the only vaccine with an indication against vaccine type pneumonia for the 20 serotypes.

For IBRANCE, we continue to be pleased by the double-digit growth in international markets and are encouraged by signs of recovery in several key markets. In the U.S., Ibrance continues to be the leading CDK4/6 inhibitor, with 83% total patient share and 73% share of first-line metastatic new patient starts. While total prescription volume was stable in the second quarter, paid demand for Ibrance was down due to increased enrollment in our patient assistance program, which we referenced last quarter. This resulted in a second quarter revenue decline in the U.S. of 7% compared with the year-ago quarter.

Inlyta's global revenues were up 29% operational to $257 million, primarily reflecting increased adoption in the U.S. and developed Europe of combinations of certain immune checkpoint inhibitors and Inlyta.

Xtandi in the U.S. was up 14% to $303 million, driven by strong demand across all approved indications. Our global biosimilars revenue grew 88% operationally to $559 million, driven by several recent oncology biosimilar launches. As you can see, biosimilars have become a meaningful part of our business while delivering lower-cost patient care options that can help reduce overall health care spending levels.

Now let me share 2 brief updates from our JAK Inhibitor portfolio. We continue to remain confident in the importance of the JAK inhibitor class for appropriate patients with inflammatory diseases given the role of JAK pathways in inflammatory processes. In addition, we have taken a targeted approach to developing selective JAK inhibitors based upon our extensive knowledge of JAK biology, coupled with our medical chemistry capabilities, that suggests the best target for a specific indication.

We believe this approach may optimize the benefit-risk profile. Of course, patient safety is of utmost importance, and we continue to monitor all compounds in our portfolio to identify signals both in development as well as after regulatory approval.

Global Xeljanz' revenue were down 9% operationally in the quarter to $286 million, driven primarily by a 15% decline in the U.S., while prescription volume increased 2%. This revenue decline reflects an unfavorable change in channel mix towards lower-priced channels and continued investments to improve formulary positioning and unlock access to additional patient lives. Also, a negative impact on new patient starts, resulting from an ongoing review by the FDA of safety data from the post-marketing ORAL Surveillance study of Xeljanz in subjects with rheumatoid arthritis who were 50 years of age or older and had at least 1 additional cardiovascular risk factor. International developed markets achieved 11% operational growth in the same quarter.

The FDA recently notified Pfizer that it would not meet the Prescription Drug User Fee Act, the PDUFA, goal date for the supplemental New Drug Applications for Xeljanz, Xeljanz XR for the treatment of adults with active ankylosing spondylitis. No revised PDUFA goal date has been set for these NDAs -- supplementary NDAs.

The FDA also recently notified Pfizer that it would not meet the PDUFA goal date for the New Drug Application for abrocitinib for the treatment of adults and adolescents with moderate to severe atopic dermatitis. The FDA cited its ongoing review of Pfizer's post-marketing safety study, ORAL Surveillance, evaluating tofacitinib in patients with rheumatoid arthritis as a factor in the extension. No revised PDUFA goal has been set by this NDA -- for this NDA.

Now I'm going to touch on the Biden Administration's recent Executive Order on promoting competition. While I believe there may be better alternatives that some of these policies put forward in the Executive Order, we can agree that fostering competition and lowering cost for patients should be the focus of any regulatory or legislative action. We continue to support more affordable options for patients, like biosimilars, improving the Medicare program to cap out-of-pocket costs, and also lower cost saving for seniors and making insurance work by requiring that patients

share in rebate savings at the pharmacy counter. We believe these meaningful solutions would have an immediate impact for patients without sacrificing future innovation.

Overall, I believe the second quarter was a clear and part of demonstration of the capabilities of the new Pfizer. Looking forward, we intend to build upon these successes by continuing to follow the science, trust in our people and remain focused on delivering breakthroughs for the patients we serve. As such, we continue to expect a revenue CAGR of at least 6% on a risk-adjusted basis through the end of 2025 and double-digit growth on the bottom line.

I would note that these projections do not include any potential impact from our COVID-19 vaccine, recent or subsequent business development activities or potential future mRNA programs. We remain very confident in our ability to achieve these growth rates because of the strength of both our current product portfolio and our R&D pipeline. At the same time, we will continue to pursue business development opportunities with the potential to further enhance our long-term growth prospect.

Just last week, we announced a global collaboration with Arvinas to develop and to commercialize ARV-471, an investigational oral product, estrogen receptor protein degrader. The estrogen receptor is a well-known disease driver in most breast cancers. And we are excited to work with Arvinas on the first potential product for breast cancer, which with its encouraging early clinical data has the potential to become a novel hormonal therapy backbone for HR-positive breast cancer.

Now I will turn it over to Mikael to speak more about our R&D efforts. And then, of course, Frank will provide financial details on the quarter and our outlook for the remainder of 2021. Mikael?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Thank you, Albert. I'm delighted to share some highlights from Pfizer's R&D pipeline, which continues to be one of our greatest strengths.

Today, I will share updates on 8 select programs in which we are pursuing first-in-class breakthrough science and which have estimated approvals before 2030 and the potential to have a profound impact on millions of patients. Last week, we announced a global collaboration with Arvinas to develop and commercialize ARV-471, potentially the first PROTAC or PROteolysis TArgeting Chimera, estrogen receptor protein degrader. 471 represents breakthrough drug design technology.

PROTAC protein degraders efficiently eliminate rather than inhibit disease-causing proteins. To our knowledge, 471, which was designed to be an oral, high-potency estrogen receptor degrader with a favorable safety profile is the only ER-targeting PROTAC degrader in clinical development and has a distinct mechanism action from the many SERDs in development.

In the future, novel assets like 471 have the potential to be the new endocrine therapy backbone, either alone or in combination with CDK inhibitors, such as IBRANCE, other targeted therapies and/or therapies with novel mechanism of action. Early clinical data show 471 has the potential to be an endocrine therapy of choice across treatment settings in breast cancer.

471 is being evaluated as a treatment for metastatic breast cancer in a Phase 1 dose escalation study, a Phase I1b combination study with IBRANCE and a Phase 2 monotherapy dose expansion study. Starting in 2022, we expect to initiate Phase 3 studies across lines of therapy in metastatic breast cancer, including in combination with IBRANCE, followed by pivotal studies in the early breast cancer setting.

Let me share some of the preclinical data that has us excited. The chart on the left shows 471 demonstrated impressive antitumor activity in combination with IBRANCE/palbociclib in preclinical studies. In the Phase 1 interim analysis was 21 patients, 471 demonstrated a compelling efficacy signal in heavily pretreated patients, the majority with prior fulvestrant treatment and all with prior CDK4/6 inhibition treatment.

The images on the right show 1 patient on 471 monotherapy who had a confirmed partial response of the 4 cycles with a 51% reduction in target lesion size, as indicated by the arrows. 2 patients had unconfirmed partial responses, and 1 patient demonstrated stable disease with more than 50% target lesion shrinkage. 5 paired tumor biopsies demonstrated ER degradation up to 90%, with an average of 62%.

The next program is ROBO2, details of which we have not shared previously. No disease-specific treatment are currently available for focal segmental glomerulosclerosis or FSGS for short. We have developed in collaboration with Boston University and Boston Medical Center a potentially novel and first-in-class disease modifying biological therapy comprising a SLIT-2 ligand antibody Fc trap that lowers activation of the ROBO2 receptor for treating FSGS as well as adjacent renal glomerulopathies.

Preliminary results from an interim analysis of our ongoing Phase 2a study in adult patients with steroid-resistant FSGS demonstrated promising data with a statistically significant and clinically meaningful reduction in urine protein to creatinine ratio or UPCR. We are advancing the program to potentially demonstrate proof of concept in '22 and preparing for pivotal studies.

This chart shows the change in UPCR, a marker of renal function, from baseline in steroid treatment resistant patients in a Phase 2a study. There was a favorable reduction in proteinuria at 13 weeks based on data from approximately half of the first dose cohort of the study. Please note, after stopping the treatment as per study protocol, the UPCR deteriorated, indicating the need for continuous therapy. Treatment every 2 weeks was well tolerated with no significant safety signals to date.

Next, let's turn to our gene therapy programs in hemophilia A and B and Duchenne muscular dystrophy. Pfizer continues to advance the broadest late-stage gene therapy portfolio of potentially transformational treatment. We expect Phase 3 interim analysis for all 3 programs in '22. In a Phase 1/2 hemophilia A study, we have seen durable expression of Factor 8 through 78 weeks, with an annual bleed rate in the first 52 weeks of 0.

In a Phase 1/2 hemophilia B study, we have seen sustained expression of Factor 9 activity into year 4 of the Phase 1/2 long-term follow-up study, with an annual bleed rate of less than 1. In a Phase 1b Duchenne muscular dystrophy study, statistically significant expression of mini-dystrophin and a 35-point increase in the North Star Ambulatory Assessment score have been observed.

Now we'll turn to our Lyme disease vaccine, the only active Lyme vaccine candidate in clinical development today, being co-developed with Valneva. The ongoing Phase 2 study, which completed recruitment of adult and pediatric participants last week, will evaluate the optimal vaccination schedule for use in Phase 3. We expect potential proof of concept in January '22 and a Phase 3 study in the first half of '22.

This chart shows that more than 90% of subjects seroconverted to all 6 serotypes with a 3-dose vaccination schedule at 0, 2 and 6 months in the Phase 2b study, demonstrating a favorable immune response.

Our respiratory syncytial virus vaccine is the most advanced bivalent protein-based vaccine with Phase 2 data published, showing high neutralization titers against both RSV A and B subtypes, which has not been demonstrated in clinical development by a monovalent prefusion F vaccine. We have been advancing these assets for both adults through direct vaccination and infants through maternal immunization.

Today, I will focus on adults. In 2020, we initiated a Phase 2a study to evaluate the safety, immunogenicity and efficacy of the recombinant RSV pre-Fusion vaccine in a virus challenge model in healthy adults, 18 to 50 years of age. I will show you data on the next slide, which we plan to submit for peer-reviewed publication soon.

Results from a Phase 2 challenge study of 62 subjects show the vaccine was 100% effective against mild-to-moderate symptomatic infection. And most participants in the study experienced minimal to no side effects. As a performance benchmark, the Ad26.RSV preF vaccine showed 52% observed efficacy in the same human challenge model.

In this slide, we show very favorable protective changes of the vaccine on viral load, left side, and in reducing drastically RSV disease severity, right side. Based on these overwhelmingly positive data, we will accelerate the development of our RSV vaccine in adults. We plan to initiate a global Phase 3 trial in the third quarter and hope to conclude the study swiftly in part due to the recent spike in RSV infections reported by CDC.

The swift delivery of the world's first mRNA-based vaccine made a scientific opportunity of mRNA technology clear. Our strategy to advance and unlock the full potential of mRNA is focused in 3 core areas. We're strengthening the core COVID-19 vaccine franchise, growing an infectious disease vaccine pipeline, and exploring therapeutic areas, like rare disease and oncology, with the strongest potential.

Let's start with the mRNA flu vaccine, which we began working on with BioNTech in 2018. Having a flu vaccine with much better efficacy, better T cell, and innate immune responses and more timely manufacture soon after strains are known could dramatically change trajectory of disease. We are projected to start first in human trial for a modified RNA or modRNA flu vaccine in the third quarter subject to regulatory approval.

Preclinical studies were performed with a first-generation modified mRNA tetravalent flu vaccine, and the data were compared to data from a marketed FLUAD vaccine. Immunogenicity in mice for a first-generation modRNA flu candidate across the 2018-19 northern hemisphere strains were higher or as high as the trivalent adjuvanted subunit vaccine. We are encouraged by these data and look forward to progressing this program.

We now turn to our COVID-19 vaccine program in collaboration with BioNTech. The Delta variant, which is the most transmissible we have yet seen, is expanding rapidly worldwide and now represent approximately 83% of sequence cases in the U.S. We continue to believe it is likely that the third dose booster may be needed within 6 to 12 months after full vaccination to maintain the highest level of protection. And studies are underway to evaluate the safety and immunogenicity of a third dose.

We are in ongoing discussion with regulatory agencies regarding a potential third dose boost of current vaccines, and assuming positive results, anticipate an emergency use authorization submission as early as August. Pending regulatory approval, we'll also plan to start an immunogenicity and safety study in August to evaluate an updated version of our vaccine, specifically designed to target the Delta variant.

Here, we show initial data from a small number of patients receiving a third dose of existing vaccine. We observed a significant boost in neutralizing antibodies following a third dose of the current vaccine for both wild type and the Beta variant. At 8 months postdose 2, antibody levels start to decline from earlier peak. In our initial analysis, a third dose given more than 6 months after the second dose elicited neutralizing antibodies, which are more than 5x higher than the wild type and more than 10x higher against the Beta variant than of the 2 primary doses.

The third dose elevates the neutralizing antibodies in our laboratory studies up to 100x higher levels post dose 3 compared to pre-dose 3. Just as we saw in the analysis of neutralizing antibodies from those in the original Phase 3 trials, the levels in the older population were comparable to the younger population.

Here, we show new breaking data from a small number of participants that the third dose boost with the current vaccine elicited neutralizing titers that when tested against the Delta variant were more than 5-fold post-dose 2 in younger people and more than 11-fold post-dose 2 in older people. Receiving a third dose more than 6 months after vaccination, when protection may be beginning to wane, was estimated to potentially boost the neutralizing antibody titers in participants in this study to up to 100x higher post-dose 3 compared to pre-dose 3. These preliminary data are very encouraging as Delta continues to spread.

Finally, let's turn to our potentially first-in-class COVID-19 antiviral protease inhibitor. If successful, our protease inhibitor has the potential to provide patients infected with COVID-19 with a new oral therapy that could be prescribed for a 5-day treatment course at the first sign of infection before patients are hospitalized or in critical care. For patients who are in close contact with someone who contracts COVID-19, we will study both 5- and 10-day post-exposure prophylaxis courses. The goal is to reduce SARS-CoV-2 viral load, thereby hopefully decreasing or preventing symptoms of COVID-19 and minimizing the risk of hospitalization.

In July, we initiated a Phase 2/3 trial to evaluate the efficacy, safety and tolerability of the orally administrated protease inhibitor in participants with COVID-19. If successful, we project a potential U.S. Emergency Use Authorization submission in the fourth quarter. Our protease inhibitor exhibits potent, selective in vitro antiviral activity against SARS-CoV-2 and other coronaviruses and potentially all currently known COVID-19 variants.

It also has demonstrated a robust preclinical antiviral effect on cells and in SARS-CoV-2 infected animals, enabled by selectivity that is more than 100x higher for coronavirus 3CL proteases than human proteases. The chart on the left shows robust dose-dependent reductions in disease microscopical scores in mice.

In Phase 1 human studies today, we have seen desirable drug exposure, good tolerability and no safety findings up to a dose of 500 milligrams twice a day over 10 days in healthy volunteers. The chart on the right of the Phase 1 pharmacokinetic study shows high drug exposure over the entire treatment period, exceeding greater than 5x the exposure predicted to inhibit SARS-CoV-2 viral replication.

This concludes our review of 8 selected breakthrough programs among many more to come this decade. Now let me turn it over to Frank.

Frank A. D'Amelio - *Pfizer Inc. - CFO & Executive VP of Global Supply*

Thanks, Mikael. I know you've seen our release, so let me provide a few highlights regarding the financials. The COVID-19 vaccine again had a dramatic positive impact on our quarterly results, and Albert has already addressed the key points on the COVID-19 landscape.

Looking at the income statement. Revenue and Adjusted cost of sales was significantly impacted by COVID-19 vaccine sales and the associated 50% gross profit split with BioNTech, which we recognize on the cost of sales line. Revenue increased 86% operationally in the second quarter of 2021, driven by COVID-19 vaccine sales and solid performance from a number of our other key growth drivers. And looking at the revenue growth excluding the COVID-19 vaccine contribution from direct sales and alliance revenues, I want to reiterate what Albert said in that we saw a continuation of solid performance from the business again this quarter, delivering 10% operational growth despite a negative 4% impact from price.

This nicely supports our projected revenue CAGR of at least 6% through the end of 2025. Of course, there will be some variability in quarterly growth rates due to a variety of factors, but we continue to expect at least 6% through 2025. There was no impact from the number of selling days in the quarter as compared to the year ago period, like we saw in our first quarter, where we had more selling days compared to the year ago period. I'd remind you that the offset to this imbalance will be seen in the fourth quarter results, where we have fewer selling days as compared to the year ago quarter. For the full year, this results in essentially the same number of selling days in 2021 as 2020.

The Adjusted cost of sales increase shown here reduced this quarter's gross margin by 19 percentage points compared to the second quarter of 2020, which primarily reflects the impact of the COVID-19 vaccine, gross profit split and applicable royalty expenses, in addition to much smaller impacts from foreign exchange and product mix.

Adjusted SI&A expenses increased, owing to a more normalized level of promotional and sales force activity, along with some impact from foreign exchange. The increase in Adjusted R&D expense this quarter was driven by increased investments in the COVID-19 vaccine and antiviral programs as well as other programs within our pipeline.

Given the tax effect of increased COVID-19 vaccine revenue, our tax rate (technical difficulty), which will impact our guidance, which will I speak to -- which I will speak to in a minute. Reported diluted EPS for the quarter was up 58% compared to the year ago quarter, while Adjusted diluted EPS grew 73% for the quarter. Foreign exchange movements resulted in a 6% benefit to revenue as well as a 6% benefit or $0.03 to Adjusted diluted EPS.

Now let's move to our revised 2021 guidance. We've again provided total company guidance, which includes the business with the COVID-19 vaccine, and then we provided some additional subledger detail on our assumptions regarding the projected COVID-19 vaccine contribution. So you can also see our projection for the business without the COVID-19 vaccine.

Our revenue projection has increased. And we now expect it to be in the range of $78 billion to $80 billion, with the COVID-19 vaccine revenue for the year being projected to be approximately $33.5 billion based on contracts signed through mid-July. I note that this projection does not include the doses with our contract with the U.S. government announced last week.

For Adjusted cost of sales, the range has increased to between 39% to 40%, which incorporates the incremental anticipated COVID-19 vaccine revenue, which has a significantly higher cost of sales due to the gross profit split with BioNTech as compared to the rest of the business. The projected COVID-19 vaccine revenue as a percentage of total company revenue at the midpoint has increased to 42% as compared to 36% in our previous 2021 guidance.

On Adjusted SI&A, we have made a small increase to the projection. We now expect $11.5 billion to $12.5 billion. In addition, we increased our Adjusted R&D guidance range to $10 billion to $10.5 billion to incorporate anticipated spending on incremental COVID-19-related programs and other mRNA-based projects that are not part of the BioNTech collaboration.

Given the tax effect of increased COVID-19 vaccine revenues, we are increasing our projected tax rate for the full year to approximately 16%. This yields an increased Adjusted diluted EPS range of $3.95 to $4.05 or 77% growth, at the midpoint compared to 2020, including an expected 4% benefit from foreign exchange.

Let me quickly remind you of some assumptions and context on the projected COVID-19 vaccine contribution and our collaboration agreement. As discussed earlier, the Pfizer-BioNTech COVID-19 vaccine collaboration construct is a 50-50 gross profit split. Pfizer books the vast majority of the global collaboration revenue, except for Germany and Turkey, where we receive a profit share from BioNTech, and we do not participate in the China region. We now expect that we can manufacture up to 3 billion doses in 2021, subject to continuous process improvements, expansion of current facilities and adding new suppliers and contract manufacturers.

As of mid-July, we have contracted for approximately 2.1 billion vaccine doses for delivery in 2021, which drove our projection of approximately $33.5 billion in revenue for the year. Our cost of sales for the COVID-19 vaccine revenue continues to include manufacturing and distribution costs, applicable royalty expense as well as a payment to BioNTech, representing the 50% gross profit split. We continue to expect that the adjusted income before tax margin for the COVID-19 vaccine contribution to be in the high 20s as a percentage of revenue. This margin level also includes the anticipated spending on additional mRNA programs.

Let me add that if we contract the delivery of additional doses during the year, we will provide a guidance update in our subsequent earning releases. If we remove the projected COVID-19 vaccine contribution from both periods, you will see that we slightly increased the 2021 revenue range to $45 billion to $47 billion, representing approximately 7% operational revenue growth at the midpoint.

In terms of Adjusted diluted EPS, without the contribution from the COVID-19 vaccine, we have increased the range to be between $2.55 and $2.65 for the year, which represents approximately 11% operational growth at the midpoint. These growth rates are all consistent with how we've been publicly positioning the business post- the Upjohn separation. And going forward, we will continue to maintain a prudent stance toward our capital allocation activities, with the opportunities for deployment shown here on this slide.

In summary, a strong quarter and first half of the year, and we have increased our revenue and EPS guidance for the remainder of the year. In addition, we've had pipeline advances and just completed a very promising business development agreement with Arvinas.

I'll now turn it over to Chris to start the Q&A session.

Christopher J. Stevo - *Pfizer Inc. - Senior VP & Chief IR Officer*

Thank you, Frank. Operator, if we could have the first question, please.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question comes from the line of Kerry Holford from Berenberg.

Kerry Ann Holford - *Joh. Berenberg, Gossler & Co. KG, Research Division - Analyst*

A few questions on the COVID vaccine, please. Firstly, a point of clarification, can I just check the upgraded 2021 sales guidance for the vaccine reflects only the doses you expect to deliver this year and not for those contracted to delivery in 2022?

As it stands today, could you talk directionally about how you see 2022 COVID vaccine sales relative to this new guidance figure for 2021? Do demand for those orders you've secured require delivery of the new updated version vaccine you referenced, the COVID -- the Delta variant?

And then finally, can we assume the price per dose in the most recent order from the U.S. government is equivalent to prior U.S. orders? And how does that pricing compare in the ex-U.S. contracts that you've more recently signed?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you very much, Kerry. Maybe I can give you an answer to that. As Frank said in his remarks, in 2021, we provided guidance for approximately 2.1 billion doses. These are confirmed orders with contract signed. We have said repeatedly that we expect to have a 3 billion doses manufacturing this year. And we are, of course, discussing about those doses, and most of them are in very advanced discussions. So I believe that we will eventually allocate all doses.

Now keep in mind that in the second half, as we said, the very big number of doses will go to middle-income countries where the price is very, very different, almost half, and to low-income countries, and lower and mid and low-middle-level countries where we provide the doses on a not-for-profit basis. So you need to take that into consideration.

The second thing that you need to take into consideration is that our financial calendar is not the exact like the political calendar, which means that December sales will not be going to 2021 if it is international. It is going to go to 2022. This is how our financial calendar works. Only the U.S. sales of December will be accounted in this year, and it will be a significant number of doses that will be allocated in December as part of the 3 billion doses.

How the 2022 looks like? It's very early to see. We have multiple countries that they have already accomplished agreements for 2022 and 2023, like Europe, for example; Israel; Canada. Canada actually, they have also -- will be going all the way to 2024. U.S. just got an additional 200 million doses. And virtually every country in the world right now is discussing with us for additional doses. Our total expected capacity for 2022, it is 4 billion doses. And I believe given the needs that, that likely will be allocated to the entire world.

Then you asked a question about the Delta variant, and maybe I will ask Mikael to provide a view on that.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Thank you, Albert. As you noted in the presentation, all data right now point to that the current vaccine is highly effective against Delta variant. They may be waning over time as often is seen with the vaccines. And that's why we shared today that if you do give a third dose boost of the current vaccine, you seem to regain very high neutralizing antibody against Delta.

We are also producing a Delta variant-specific vaccine mainly to make sure we cover all options of the future, but we remain highly confident in that the current vaccine when used appropriately will be effective against Delta, and we are in dialogues with regulatory agencies about this potential of a third dose of a vaccine, pending epidemiology of the vaccinated over time. Thank you.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you very much, Mikael. And Kerry, also on the price per dose, we do not discuss our prices with each individual country, but we have given our overall policy, which says that the high-income countries, they have comparable prices, but they vary only based on -- we give discounts to these prices based on the volumes that are committed. Middle-income countries have approximately half of that price. And for the lower middle- and low-income countries, we are providing our vaccines at a not-for-profit basis. Thank you.

Operator

Your next question comes from Matthew Harrison from Morgan Stanley.

Matthew Kelsey Harrison - *Morgan Stanley, Research Division - Executive Director*

Great. A few, if I may. First, on the regulatory outlook for the JAK. Do you have any idea on how long the FDA may continue to review the file or when we might expect to see some response on next steps there?

And then second, on the mRNA flu vaccine. Can you comment on the potential regulatory picture there? Do you think you may be able to get that approved just based on titers? Or do you think you'll have to actually run a head-to-head study versus the existing flu vaccines?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Mikael, I think you could take those 2 questions, and then maybe if Angela wants to add something on the JAKs.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Yes. Thank you. Well, as you know, FDA and other agencies are reviewing both existing and new JAKs. In FDA, we are waiting for them to conclude final assessment of the surveillance study. And during that period, they have passed PDUFA timeline for both us and others to develop new JAK. We certainly hope, as the workload from COVID may attenuate, that the agency will have soon been able to review all available data as we do consider that JAKs have a really meaningful and important role in management of RA properly used in the right patients and also new indications where there are fewer alternatives such as atopic dermatitis, alopecia, vitiligo and so on. So we cannot give any firm timelines, but we certainly hope it will be relatively soon.

For the mRNA flu vaccines, we plan to start our first in human studies shortly based on some of the encouraging data we showed from preclinical studies. We will both run immunogenicity study as well as head-to-head study. Given the high potency of the mRNA, we are optimistic, and we believe there is a good opportunity that one can create a premier vaccine with superior efficacy versus existing flu vaccine. That's why we think not only to demonstrate high titers, but also demonstrate superior efficacy would be very valuable, and we are gearing up using all our experience to run trials first to look at the time schedule for both immunogenicity and head-to-head event trial.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Angela, do have anything to add?

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

I think Mikael covered all the key points. Just to reassure everyone that we are in constant communication with the FDA. And they're just doing their risk-benefit analysis like as they would with any and all molecules. And so we're very confident that there is a role that our JAKs do play. And we just -- we are waiting eagerly for the response from the FDA, so, thank you.

Operator

Your next question comes from Daniel Busby from RBC Capital.

Daniel James Busby - *RBC Capital Markets, Research Division - Assistant VP*

I've got 2. First, on the COVID-19 vaccine. I think it's fair to say that Pfizer has been a bit more outspoken about the likely need for recurring booster doses than CDC and FDA, at least at this point in time. Can you provide any additional color about why that's the case? Is this simply a matter of

letting the data catch up to what you view as a likely eventuality? Or is it a function of Pfizer and regulatory agencies interpreting the data that we have today perhaps differently?

And second, with respect to Prevnar 20, can you talk a little bit about your expectations for October's ACIP meeting? And what you would characterize as a good outcome for the adult-use vote?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Maybe I can give you the answer to the COVID, and then Angela can take the Prevnar 20.

I don't think that there is different interpretation of data between us and regulatory authorities around the world. Actually, there is a extremely good collaboration and the same interpretation. I think what we have said is not new, i.e. for months, I'm saying that we believe, based on the data that we receive holistically, but we will need a booster 8 to 12 months and -- from the second dose. And we have seen that with the Delta, that might be needed a little bit earlier, particularly for some parts of the population. But we haven't submitted the data yet. So I don't think that FDA or CDC can speak because they have very different authority when they speak. It's extremely -- they have very different considerations. So we will submit those data by August 16. They are aware of them.

And the FDA needs to review them and then provide or not their approval. And then once it is approved, third dose booster, then CDC needs to understand the situation in the country at that for a period of time. And they will have to make a recommendation about the booster. So the same happens in different countries, and it depends on what percentage of the population have been vaccinated earlier in the year or later in the year. They may have very different sense of urgency. Clearly, countries that gave big percentage of their population in the January, February timeframe, they have very different urgency because the time is -- the clock is ticking.

And with that, I will go to Angela about the Prevnar 20 and ACIP.

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

Yes. Thanks. Thanks, Albert. Well, you heard Albert talk about the very differentiated label that we do have with Prevnar 20 in his opening comments. And just to reinforce that the 20 serotypes and the coverage that -- the broad coverage that provides, but also, the fact that our label contains an indication for both IPD as well as pneumonia is really unique. And I think that this pneumonia indication is the true strength of the Prevnar family, being that we're the only company that has the 80,000 capital trial where this pneumonia indication was based.

And so with this, what we anticipate coming up in October are policy questions that will be addressed for both PCV20 as well as the Merck 15. And we have an early read into this already because at the last ACIP meeting, different policy questions were posed for both products. For Prevnar 20, there's a question around vaccinations of 65-plus as well as 50-plus, in addition to the 18 to 49 or 18 to 59 immunocompromised. For Merck 15, the age range and the policy question posed there was for 65-plus.

So when you look at what's different, the -- only Prevnar 20 was being looked at for the 50-plus. So we'll have to see how all this ends up, and we're looking forward to having a robust discussion at the October ACIP. But I think that the setup of these policy questions give us a good view into what the discussions will look like and what the outcomes might be. So thanks for the question.

Operator

Your next question comes from Chris Schott from JPMorgan.

Christopher Thomas Schott - *JPMorgan Chase & Co, Research Division - Senior Analyst*

Just coming back to the COVID-19 booster. Would you envision this as an annual booster? Or with these levels of antibody titers, would you envision that third dose could give more sustained protection against COVID just thinking about just kind of how the market evolves over time?

And then my second question was just coming back to the JAKs, and just 2 more detailed questions. First, any change in thinking as we think about abrocitinib, the 100-milligram versus the 100- and 200-milligram approvals? I don't see anything you've learned with regulatory interactions, et cetera, that's changed your view there. And then maybe second question on the JAKs is just with Xeljanz. What would an EMEA-like label revision mean for Xeljanz as we think about the U.S. commercial opportunity?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Yes. Mikael, I think you can take the booster in terms of, is it a third dosing done, you think? Or it's going to be an annual revaccinations? And then, Angela, we move to you for JAKs and Xeljanz.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Thank you. Well, Albert spoke earlier to the importance of both following vaccine efficacy in different regions of the world and enter new strain. Right now, we have a surge in the Delta strain. It's the most infectious strain ever seen, and it puts pressure on vaccinated individuals. The data we showed today indicate at 6 to 8 months, we can boost up to 100-fold the antibody titer after the dose compared to pre-dose.

At the same time, we hear reports from various parts of the world, real-world evidence that they do see some breakthrough cases of the Delta variant in vaccinated. So this type of data is a typical package we will put together, in this case, for August submission, as Albert alluded to, for a third dose. We will continue to monitor and generate data on the impact of a third dose, which we do have ongoing in our Phase 3, and possibly soon also in real-world evidence. We expect the third dose to be potent and somewhat maybe more long lasting than the second. But we also recognize that the virus constantly evolves. And you all start to notice about Delta Plus variant.

Hence, while I cannot predict with certainty the future, I would not be surprised if similar to flu, that we would need with interval to boost our vaccine against COVID. Whether this will be on an annual or based on simple diagnostic that allow it to be boost at the right time before your risk for infection is high, we need to monitor. But all in all, we believe that similar to a flu business, it may be likely for the COVID business. But we are gathering data to validate, and we'll constantly work with key opinion leaders and regulators in interpreting the data.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Angela?

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

Great. I'll start with abro. The conversations and the discussions that we're having with the FDA, as it pertains to abro, have been consistent. And at this point, as we've discussed earlier, we're just waiting and waiting to hear from them as to their -- sort of their points of view. But both doses are still in discussion. And I think, ultimately -- I think, ultimately, where you might be going with your question is sort of what happens if we only get one or the other. And I just want to reinforce that we are very confident in the potential of abro, whether it's for both doses or for one.

And the reason is that we come back to just the size of the market. We've discussed this before, but there is a very, very large market with a huge unmet need. There's [16 million] (corrected by the company after the call) patients 12 and up with atopic dermatitis. Only 4 million of those are being treated today with any systemic therapy. And because this is such a heterogeneous disease, patients really need different options. And so we're really looking forward to hearing back from the FDA. But we believe that the risk-benefit profile of abrocitinib is going to have a role in the treatment of atopic dermatitis patients. And it will be a welcomed addition and an additional option that patients really need.

And then coming back to Xeljanz, you had a question around our EU label. So actually, the changes to the EU label were posted in June, although we're still waiting for the final SPMC -- SmPC, excuse me. And there, the label is really looking at a cautionary note. For those who are 65 plus, who are smokers or have malignancy risk, and the caution there is for physicians to consider alternative therapies prior to using Xeljanz. And so I think this is pretty consistent with how Xeljanz is being used today.

If you look at where the utilization is, more than half of our business is in third-line treatment, which is after the utilization of other treatments like biologics. So again, I think we'll wait to see how this plays out. But the fact that it is being recommended for third line is very consistent with how it's being used today.

Operator

Your next question comes from Ronny Gal from Bernstein.

Ronny Gal - *Sanford C. Bernstein & Co., L.L.C. - Senior Analyst*

The first one will also be on the boosters. I fully understand this point around the third dose increasing antibody titers significantly. The counterpoint that has been raised is that the third dose is not needed because while antibodies wane immunity against severe disease is not or at least have not so far waned over time. Can you discuss a little bit how you see the waning of immunity in the large public and the elderly as you're seeing it for the -- your vaccine even if antibody dose comes down?

The second question is around biosimilar business. This is something you highlighted. We are not really seeing a lot in the pipeline as a clinically available pipeline for your biosimilar business beyond the Humira biosimilars. Can you discuss your plans for that business? Are you -- is this still the emphasis for Pfizer? Or are you deemphasizing that?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Ronny. Mikael, again, I think I will ask you to make comments on if we see waning of immunity also in a severe disease or in hospitalizations, and we have seen data about that. Mikael?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Yes. Thank you, Albert. It's a very good question. So first, we do see more -- after 6 to 8 months, more rapid waning concerning infections and mild to moderate symptoms. Those are likely entirely, or to a large degree, dependent on antibodies. And the drop in titer that we alluded to, if you raise it, may have a good probability to reverse that waning. Fortunately, the protection against severe disease, hospitalization and fatal outcomes remains pretty high, but we do see some lowering, particularly in real-world evidence studies from Israel, we see some lowering in that protection in risk groups, such as older adults, immunocompromised.

That's likely because in addition to antibodies, T cells help out in keeping up strong defense against severe disease, which is later in the infection process, and particularly when antibodies have waned. But slow, but still noticeable gradual decline in protection also against severe disease is something that's on our eyes. And certainly, we believe that by boosting you may strengthen antibodies and T cells. And you have an early warning signals whether to do that with some modest waning in hospitalization given its risk of severe outcome or wait in your interpretation of that.

All in all, I think a third dose would strongly improve protection against infection, mild-moderate disease, and reduce the spread of the virus, but also give you some extra muscle and reverse the slower decline against severe disease. So this is how we're looking at it from multiple angles in order to describe the full opportunity with boost.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Mikael. Angela?

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

Thanks for the question on the biosims. And certainly, we've been so pleased with the tremendous growth that we've seen in this area and the deep utilization of our biosims. I will say that for our biosimilar portfolio and where we see it today, since we've made this pivot to a pure play sort of innovation focus in our pipeline, we are really now looking at that biosimilar portfolio vis-a-vis other investments in breakthrough therapies that we have to make.

So of course, we will continue to look for opportunities. But I would say at this point, it's going to be more opportunistic and that we're really looking at our investment in our development program to be competitive and to be -- to make sure that we have the ability to focus on breakthrough therapy. So I'd say that, going forward, we'll be more opportunistic because we're just weighing and trading off so many incredible programs on the innovative side that we could also be doing.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Angela. And also, you need to take into consideration, Ron, that we have right now so much substrate in our R&D pipeline and so much opportunity to invest. But right now, we are clearly focusing on first-in-class, and particularly best-in-class, first-in-class. And there are so many, right? So that's why R&D budget is increasing. So thank you very much. Back to you, Chris.

Christopher J. Stevo - *Pfizer Inc. - Senior VP & Chief IR Officer*

Thank you, Albert. Operator, next question, please.

Operator

Your next question comes from Geoff Meacham from Bank of America.

Geoffrey Christopher Meacham - *BofA Securities, Research Division - Research Analyst*

Just have 2. For Mikael, on COVID boosters, when you look at the new cases of the Delta variant, the protection varies quite a bit in vaccinated individuals, really depending on geographies around the world. So are there common themes that you've identified that could explain this? And what can you say about the T cell dynamics from the vaccine over time?

And then second question, for Albert or for Frank. Just given the guidance hike from the COVID vaccine, does this change Pfizer's urgency or size of your capital allocation decisions? I would think that this would give you maybe more deal capacity to get over the LOE period at the end of the decade.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you very much. Let me start with that. I am sure Frank will just say the same, the second one. We always have this urgency. And this extra cash inflows do not change neither our strategic direction, not materially our ability to perform this. They still give us better flexibility, and we plan to allocate capital to develop the business with a very big sense of urgency.

Now on the COVID boosters and your question about why we see differences around geographies, in fact, actually, as Mikael will explain in a moment, the data from all geographies are consistent if you take into consideration the time element. But Mikael, please take it.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Yes, you said it very well, Albert. We first get the glimpse from real-world evidence in Israel given the very rapid massive vaccination they did over basically January to March. And January started with older adults, and those who are vulnerable, they are now 6 to 8 months, and they have a large number of them. So that's why they see the vaccine waning. And that's why they also communicate about our consideration for a third dose.

Other countries that started later and amping up their rollout slower will -- and are starting to see similar trends representing what Israel saw in June. And we are getting those reports, which tells us we are increasingly certain that what we have learned from Israel is likely to be a similar direction in many other places. Of course, we need to get all of that data in order to be fully clear about this, but the trends look similar.

Finally, there is also an element that some countries, particularly U.K., extended the interval between dose 1 and 2 to a longer interval. Likely, they will get a bit more long-lasting protection. And their data may come a few months later. The disadvantage of extending the range between dose 1 and 2 is that you expose after dose 1 many individuals to a high risk of reinfection, but you do gain likely a somewhat extended protection. So these are 2 examples, when you started to vaccinate, the time difference between dose 1 and 2. And finally, there may be, of course, some difference in care of this type of diseases in different countries. But all in all, we expect it to look somewhat similar in its direction.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

And just to clarify when Mikael says extended because the spread, the first between the second, is not that they would get more after the second. It is that the real protection starts later in -- from the second dose. And then this is the case that most of the data in the U.K., for example, are 1 to 3 months. And most of the data in Israel when received is in 3 to 6 months, and most of the cases are happening there. And we have also visibility to other data, including some data we're performing here in the U.S., but the trend is the same.

It's pointing to the same direction that you have very good protection in the beginning, then there is a waning when you come closer to 6 months, which is even more profound with Delta, and waning, it is mainly for -- is more profound for mild cases, but there is a clear waning also for hospitalizations and severe diseases. What used to be 100% in the first month, now is coming to the low 90s, and in cases to the 80s. So that's the difference between the different geographies. The time element, you will see very -- actually impressive consistency.

Operator

Your next question comes from Andrew Baum from Citi.

Andrew Simon Baum - *Citigroup Inc., Research Division - Global Head of Healthcare Research and MD*

Firstly, in relation to Prevnar 20, could you talk to how you expect ACIP to address the current recommendations for Pneumovax? Has that dropped given the serotypes, which you are now addressing with Prevnar 20?

Second, you commented on a number of your other vaccines. You didn't comment on your C. difficile candidate where the primary endpoint is rapidly approaching. Could you just comment on your relative degree of optimism or not for that vaccine?

And then finally, in relation to the patient assistance program for IBRANCE. Just looking at the script trends for Verzenio versus IBRANCE, there's clearly a disconnect there. It could be due to the patient assistance programs. But it will be helpful to know the magnitude of which the PAP contributes and how that has changed over the last 6 months or so?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you. Mikael, you want to take first this question. You didn't speak about. I think it was C. difficile you referred to.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Yes, yes.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Are you losing confidence? Why you did that?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Well, we had such a rich pipeline. And we thought that we wanted to allow you to have questions to and not speak too much ourselves. So we selected 8 assets where we thought you -- we wanted you to hear some update. C. diff, we continue with the trial. We passed one review that had 30 cases. And we're coming now to case numbers that are more sizable that you would expect to be able to relatively soon have an opportunity to determine if vaccine efficacy is robust. And you will be able to have a readout.

We are expecting this fall to have another readout in that trial, pending events. But certainly, I continue to believe it's a very well-designed vaccine. There is precedent with antibodies if you neutralize those toxins. So I continue to say be patient. We continue to mature the study. And I do hope it will have an encouraging readout. But like in any clinical study, you can never be fully certain about the outcome, but I remain very encouraged and optimistic myself.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

So thank you, Mikael. And Andrew, just to clarify, it's not that there was something behind it. It is that we have to select a few assets that we could present new data.

Angela, please take the question about Pneumovax, if -- what do you think ACIP will do and the program of IBRANCE, the path to growth?

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

Sure. Well, the question of Pneumovax is something that we can refer to in the ACIP discussion that was had recently. Again, it comes back to the policy questions that were posed. And clearly there, just to reinforce what I said earlier, which was that there were different policy questions posed for both PCV20 as well as Merck 15. The question of whether 50-plus would be vaccinated was posed only for PCV20. And specifically, your question about Pneumovax, that is being evaluated only with Merck 15, not with PCV20 or with any PCV. So again, different policy questions and very specific to each pneumococcal vaccine.

And then going to your question about the PAP usage. We are seeing this clearly as a trend that is very much aligned with the economic hardships that we're seeing as a result of COVID and the pandemic. The IBRANCE patient is a younger population. And so -- and because they're on commercial insurance, their economic status is very much then aligned to employment. And what we've seen throughout the pandemic are 2 things. One is the -- as they slow down in new patient starts, which actually is one of the reasons for this -- for the negative growth that you saw in IBRANCE in the U.S. And the second and more prominent one, this quarter, is the PAP. So I think what you're seeing here is very consistent with what we're seeing in the environment generally as it pertains to economic hardship. And so that is definitely one explanation. And then the other explanation would be a slowdown in the new patient starts that we've been seeing as well.

Operator

Your next question comes from Carter Gould from Barclays.

Carter Lewis Gould - *Barclays Bank PLC, Research Division - Senior Analyst*

I appreciate all the color on the pipeline from Mikael. A couple from us. First, you gave us a pretty comprehensive set of updates. But in terms of expectations on timing from the pediatric study, I don't believe I saw that reference. And just wanted to confirm that the recent asks from FDA haven't pushed timelines back there. And then as we think about the oral proteasome inhibitor, clearly have moved very fast there. Can you comment just around your ability to supply the market in bulk sort of out of the gates, assuming the timelines are tracking kind of how you're messaging?

And then, apologies if you guys addressed this already, but it seems like one of the things you guys do control is -- on the JAK side is the potential presentation of the JAK ORAL Surveillance data. Any color on when we might see that presented at a medical meeting?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Yes. So let me take quickly the first 2. And then for JAK, Mikael, maybe you can assist.

The pediatric study, we are -- as you said -- as we have said, we are projecting in the September timeframe or immediately after summer to be due. But FDA has asked some requirements, and we are looking at them. But our intention is to try to -- even with these requirements to try to come in the same timeframe. So we are not changing right now our expectations as to when the study can recruit. We just -- if we need to do more in less time, we will try to accommodate that. So that's the first one.

On the oral supply -- on the oral and the supply. As you know, this is not a compound that we have seen clinical efficacy data yet. So the risk is there a bit higher than anything else. But of course, the disease is moving. So I have authorized our team to invest and manufacture at risk significant quantities of the oral so that if we are successful we will have quantities for the world as much as possible. That's a significant investment that we are doing. At risk, it could go all the way to $1 billion, including some of the research work that is happening. So -- but I think it is the right thing to do, and I gave them the green light. They should not be thinking about cost right now. They should be thinking about success of the oral program.

And then for the JAK, Mikael, any -- do you know when the study will be published or the results?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

We have focus to share all the data of the study obtained this far with regulators. And as you know, conclusions have already been posted about the data from both European, like the PRAC committee, and U.S. So while there isn't a date yet when the study will be published, regulators have had access to it and have made updates. So I think the most critical element is for the U.S., European regulator finalize things. And like Angela spoke to, that will give clarity to the class of JAK and to Xeljanz and which patients with treatment lines that benefit most.

And as you know, in addition to the study, we have years -- 10 years of surveillance. And we continue to share all of that data as the study was mainly in a subset of patients with increased age and cardiovascular risk. While, of course, our surveillance carries all Xeljanz patients, and we have continued to share those robust data.

Operator

Your next question comes from Geoffrey Porges from SVB Leerink.

Geoffrey Craig Porges - *SVB Leerink LLC, Research Division - Director of Therapeutics Research & Diversified Biopharma and Senior Research Analyst*

Mikael, one for you. You mentioned the Delta Plus variant, which, of course, has picked up the K417N mutation. How concerned are you about Delta Plus? And then is there the possibility that, of course, it will pick up E484K and then be even more resistant to vaccine-induced immunity? And relative to that, do you have a view yet as to whether the best booster strategy is the original Wuhan strain, the Beta strain, the Delta strain, Delta Plus strain?

And then lastly, have you contemplated heterologous boosting with your vaccine after, for example, the ChAdOx vaccine or vice versa? Is that something you're studying?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Mikael?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Yes. Starting with Delta Plus. So right now, Delta is a very fit virus and continues to infect and dominate. It's too early to know where the end of the current Delta Plus will have transmission sufficiently to outcompete Delta. So when we say plus, it means just continue to monitor into the future. At some time point, whether 6 to 12 months, there are likely going to be strains that pick up additional mutations, but stay also fit. Meanwhile, what we have seen with the wild-type vaccine is that we see for each dose, not just a higher magnitude of antibody, but breadth, the repertoire of different cell producing antibodies grows and grows. So you seem to cover with increasing dose more variants.

If you go back and look at the slides, we used Beta variant as an example. There was somewhat of a difference after dose 2, harder to neutralize the Beta variant, after dose 2, 3 easier to neutralize the Beta variant. So that's why we, this far, find the wild-type boost very useful for existing and new variants. Now, as Albert has said before, we always want to be prepared for the unexpected, and we continue to prepare Delta and Delta Plus strains.

But right now, we do think that wild-type vaccine is going to be very efficient, but we always want to be ahead of the curve. I think the way to win this game is to keep up high immunity, reduce the amount of virus. And that's why we do both. We will study boost with existing and are prepared if ever needed to have an updated if the virus can be fit and breaks through immunity.

Finally, on the heterologous boost, there are trials coming out, performed, for example, in U.K. that showed favorable outcome for those that vaccinated with AstraZeneca on getting an mRNA boost, such as with the Pfizer-BioNTech, which they use. Those are data that you should review. And I'm sure patients and physicians will employ their own conclusion. I know there is in U.S. similar studies to benefit from that mRNA vaccines can be given repeatedly, while adenovirus delivered vaccine has limitation for repeat use.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Mikael. And again, I want to make -- to emphasize that our strategy when it comes is that we take no chances here. This is too serious to risk. So when we have a variant that it is of concern. Always we make immediately at risk a vaccine to try. We -- first time we said that was with Beta. That was seen very aggressive. So we started doing the vaccine, and we have a vaccine right now. We are going to submit it to the FDA. Eventually, we don't need it. It was very clear because after we did that, we've got data for immunogenicity, but also we got the South African study about the [100%] (corrected by the company after the call) efficacy in the Beta, although smaller numbers, but 100% efficacy.

So we know we don't need it, but we try. The same we do now with Delta. It looks like we will not need it for everything that we see so far. But we are developing one in the backstage. So in case something goes wrong, because biology is sometimes unpredictable, we will not have to wait 3

months because this is our time right now. From the day we assign a variant -- as a variant for stamping our own interpretations, we take 95 days to be able to have a vaccine. So that's why we'll always try to be ahead of the curve. But too serious of an issue to take risks. Back to you, Chris.

Christopher J. Stevo - *Pfizer Inc. - Senior VP & Chief IR Officer*

Thank you, Albert. Sylvia, next question, please.

Operator

Your next question comes from Louise Chen from Cantor.

Louise Alesandra Chen - *Cantor Fitzgerald & Co., Research Division - Senior Research Analyst & MD*

So first question I have for you, do you think a full BLA approval would actually increase vaccination rates? And do you think you might see that as early as this year?

And then secondly, how receptive do you think U.S. regulators are to a booster shot? We see a lot of conflicting headlines. So just curious what your discussions have sounded like there.

And then lastly, your RSV vaccine, you showed 100% efficacy rate. So just curious if you could elaborate more on that market opportunity for you and how big that market is in terms of sales and other metrics?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Yes. On the vaccination rates, Louise, from what I see and what we see through the different polls from people that were reluctant, it seems that this will play a role. Some people will change their reluctancy to willingness to get vaccinated if the vaccine gets full approval. And in terms of the timelines, again, I leave it to FDA. I know that they consider that a priority.

The second, how receptive regulators are on a third dose? I think regulators are receptive or not to data. And they need to see the full package of data. Once they see it, they have to speak. So I don't want to make comments about that.

And RSV, which is clearly a very, very large opportunity, but it is growing even more because of the -- we see that the epidemiology of the disease is getting more and more hot. I will ask Mikael to give us some color here.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Yes. We are very excited about the data and opportunity for an RSV adult vaccine. There are hundred thousands of cases, and they -- per year in the U.S., and they are particular, of course, difficult for -- in older adults above 60 or adults that have underlying conditions, whether chronic lung diseases or immune compromised. Now there are actually up to 15,000 deaths just in the U.S. annually. So it's not just about a difficult disease or a fatal outcome. So we think there is a very large opportunity.

Now with our vaccine, to the best of our knowledge, it's the only vaccine in late clinical trials that target RSV A and B subgroup. Please recall that the A and B subgroup variants are likely of similar quantities circulating. Some years one is larger than the other. Some years, they are equal. So we cover all of the available RSV protection by valent vaccine if shown successful in the final studies.

Also, I wanted to make it clear that when you look at the data in our RSV challenge study of the very prominent 100% protection, there are benchmarks published. And please have a look, from the adenovirus, that is also now in advanced clinical trial, which showed in the very same

model pursued by the very same U.K. Institute, half of the response, around 50%. So we think we have a potent vaccine. We have a well-tolerated and a unique aspect of covering both strains. You have some closer activity between the strains, but not as good protection unless you have both parts for the A and the B strain.

Angela, anything you want to shed light on how you commercially see this?

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

Yes. No. Thanks, Mikael. And maybe just to reinforce what Mikael said, which is that there are hundreds of thousands of older adults that are hospitalized and tens of thousands of deaths each year. In fact, this is the second leading cause of respiratory illness following flu. So we think that we have a great opportunity to, in fact, develop this market because it is quite under-diagnosed today and under-reported. And frankly, it's really in the sweet spot of what we do with adult vaccinations and also seasonal vaccinations, which go well with our Prevnar franchise. So all in all, a tremendous and exciting commercial opportunity.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you to both. As you can see, there is a lot excitement to both Angela and Mikael. And I share the same both for the size of the unmet medical need right now, but also for the capabilities of what looks like a very effective vaccine remain to be proven with the Phase 3 study, but we are going to execute with the same speed as we are doing lately our vaccine studies.

Operator

Your next question comes from the line of Terence Flynn from Goldman Sachs.

Terence C. Flynn - *Goldman Sachs Group, Inc., Research Division - MD*

Maybe I just had a 2-parter. First, just wondering if you can provide the latest point estimate on your vaccine efficacy from the Phase 3 trial. I think you gave us that number back in April. It was around 91%. And just wondering if there have been any severe cases in the vaccinated cohort.

And then on Prevnar 20, how are you thinking about that in the context of your long-term guidance? Can that actually grow your Prevnar franchise significantly? And any more detail you can provide there?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Mikael, it was, I think, 92%. Can you comment on the latest estimate and if you have seen any breakthrough?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Yes. This is a Phase 3 trial that will be very soon published on medRxiv, and it will appear in a top peer-reviewed journal. Please check in on medRxiv to get details. It may be up any day this week. It covered up to 6 months. First 2 months, 96% protection. Then above 90s between months 2 and 4, and then about 83% to 84% months 4 to 6. We have retained during that period very high protection against severe disease and hospitalization.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Angela -- Mikael and -- excuse me, Angela, about the Prevnar. Do you think you can grow it? I'm asking you to do it, but what do you think?

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

Well, I think, again, it comes back to the policy questions that have been posed already by the ACIP, which will be discussed in October. As we've said today, there are really 2 up there too. There are 2 questions being posed that are different to what we have with Prevnar 13 today, which is, number one, the ability -- should we or should we not be vaccinating those that are 50-plus? And then secondly, those that are immunocompromised, 18 to 49 or 18 to 59. Both of those populations are different to what we have with 13. So we are engaging.

And we will be engaging at the ACIP, of course, discussing our data with the relevant decision-makers and stakeholders and sharing our information. And we hope to have a positive outcome at the end of ACIP. But honestly, this is all to be discussed. And I think a little too early to speculate what could happen. We need to have a robust scientific discussion to really understand what these opportunities are.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Okay, Angela. We will give you some time to grow it. So with that, I think we've come to the end. Thank you for joining us today, for your continued engagement with Pfizer. We will really appreciate, and we learn a lot from this engagement.

Our experience with the COVID-19 vaccine had taught us a great deal about what is possible and what is impossible. And most things are possible. So most notably, it has taught us that we can drive step changes at Pfizer, not just incremental change.

To keep you updated on the progress we are making in R&D, we will host our next focused investor update later this year. A date will be announced soon. For this event, the Pfizer vaccines team will provide an update on our vaccine pipeline progress, including our plans to continue advancing our cutting-edge science in such areas as mRNA programs for COVID-19 and flu as well as the RSV research programs for both maternal and adult indications and other mRNA vaccines that we are working on.

Before we close, I want to once again thank Chuck Triano. Chuck, for his many contributions to Pfizer and for successfully elevating our Investor Relations function to a best-in-class. Chuck, you are a pro's pro. And on behalf of all Pfizer colleagues, I wish you and your family all the best in the next chapter of your life. Chuck is leaving behind some big shoes to fill, which is why we are thrilled that Chris Stevo has decided to join the Pfizer team.

Chris joins us from the Alexion Pharmaceuticals in Boston, where he was Vice President and Head of Investor Relations. He brings a wealth of experience as a buy-side analyst and portfolio manager as well as a strong network of relationships across the investment community. His deep knowledge of the health care industry would be a great asset, as we continue to advance our innovative pipeline to deliver breakthrough therapies and vaccines to patients and long-term value to shareholders.

With that, I will bring our call to a close. Thank you for joining us. Have a great rest of your day.

Operator

Ladies and gentlemen, this concludes today's call. You may now all disconnect.