### Overview of Activities in 2017

Environment Environmental Protection Society Providing Value to Society HR Human Resources Productivity Raising Productivity

ltems	Main initiatives	Main performance indicators in 2017		Examples of E
Research	<ul> <li>Continuously generating first-in-class and best-in-class drugs</li> <li>Creating molecular targeted drugs that contribute to personalized healthcare (PHC)</li> <li>Strengthening innovative proprietary research technologies and creating innovative antibodies</li> <li>Providing support and education for researchers from Asia</li> <li>Maintaining high animal welfare standards in accordance with international guidelines</li> </ul>	<ul> <li>In-house products in development pipeline: 13 (as of February 1, 2018)</li> <li>Expanded business at Singapore subsidiary Chugai Pharmabody Research Pte. Ltd.</li> <li>Academic papers and presentations at scientific conferences regarding Chugai's innovative proprietary technologies: 61 (2013-2017)</li> <li>Published academic papers regarding Chugai's research findings: 97 (2013-2017)</li> </ul>	<ul> <li>R&amp;D expenditures to revenues: 16.6%</li> <li>Created development projects using Chugai's Recycling Antibody<sup>®</sup>, Sweeping Antibody<sup>®</sup>, bispecific antibody and other proprietary antibody technologies</li> <li>Started operation of a collaborative lab at IFReC based on an agreement with Osaka University</li> <li>Conducted ongoing training on animal welfare for all research staff involved in laboratory work</li> </ul>	Environment • F • C V Society • C iii • A h f
Development	<ul> <li>Improving clinical development of drugs to address unmet medical need</li> <li>Increasing productivity and speed of global clinical development for early market launches</li> <li>Conducting simultaneous development and regulatory filing of drug therapies and diagnostics that contribute to PHC</li> <li>Strengthening lifecycle management to maximize product value</li> </ul>	<ul> <li>Pipeline projects: 41 (as of February 1, 2018)</li> <li>New products launched and new indications: 14 (2013-2017)</li> <li>PHC-based development projects: 21 (as of February 1, 2018)</li> <li>Projects in-licensed from Roche: 15 (2013-2017)</li> </ul>	<ul> <li>Projects being co-developed with Roche Group: 33 (as of February 1, 2018)</li> <li>Projects in response to development requests for unapproved drugs/indications: 7 (2013-2017)</li> </ul>	HR F fi + Productivity C +
Production	<ul> <li>Providing a stable supply of high-quality drugs and investigational drugs</li> <li>Enhancing the system for faster global launches and simultaneous development of multiple products</li> <li>Achieving early PoC by raising the level of CMC development</li> <li>Raising the level of competitive advantages from late-stage development to initial commercial production</li> <li>Achieving world-class quality control, quality assurance and regulatory functions</li> </ul>	<ul> <li>Invested in facilities for faster launches and simultaneous development of multiple antibodies and small molecule drugs (established new biological API manufacturing facility at Ukima Plant (UK3), enlarged solid formulation manufacturing facility at Fujieda Plant, etc.)</li> <li>Received FDA pre-approval inspection and approval for Hemlibra</li> <li>Strengthened global supply chain management</li> </ul>	<ul> <li>Enhanced next-generation core technologies for API manufacture and formulation</li> <li>Strengthened development ability by reducing costs from the early stage onward and planning and implementing a dosage form strategy</li> <li>Established a system for quality control functions to enhance specialization and raise operational efficiency</li> </ul>	Environment F e P Society C HR P a HR P a F F in F Productivity F a C C
Marketing	<ul> <li>Contributing to advances in medicine as Japan's leading oncology drug and therapeutic antibody company</li> <li>Promoting standards of care, regional healthcare and PHC</li> <li>Contributing to care through consulting and liaison functions</li> <li>Enhancing area promotion strategy to increase marketing productivity</li> <li>Conducting disease awareness and patient support activities in mainstay product areas</li> </ul>	<ul> <li>Share of sales in the Japanese therapeutic antibody market: 27.3%<sup>1</sup></li> <li>Share of sales in the Japanese oncology market: 20.2%<sup>1</sup></li> <li>Share of sales in the Japanese hospital market : No. 1<sup>1</sup></li> <li>Satisfaction ranking based on healthcare providers' assessments: 3rd<sup>2</sup></li> <li>Education for MRs with a high level of expertise</li> <li>Enhanced communication of safety information through use of postmarketing surveillance and adverse reaction databases and cooperation with Safety Experts</li> </ul>	<ul> <li>Enhanced marketing functions based on local characteristics</li> <li>Patient-centric support activities for regional healthcare and multidisciplinary team care</li> <li>Activities to promote appropriate use of medicines through trial service of an app that supports adherence to medication by facilitating smooth communication between patients and their healthcare providers</li> </ul>	Environment III P Society P P P P P H P P C C d d P P R P P H R P P P P P P P P P P P P P
Medical Affairs	<ul> <li>Building a consistent global medical affairs promotion system with proper independence of roles</li> <li>Strengthening systems for healthcare compliance and governance of contract-based post-marketing studies</li> <li>Conducting area-based evidence creation and promoting scientific communication activities</li> <li>Introducing global medical information functions</li> </ul>	<ul> <li>Contract-based post-marketing studies: 25 (as of January 31, 2018)</li> <li>Staff with GCP Passport (JSCTR certification): 153 (as of January 31, 2018)</li> <li>Acquired third-party accreditation for MSL certification program from the Japanese Association of Pharmaceutical Medicine</li> <li>Number of joint preclinical studies: 11 (as of January 31, 2018)</li> </ul>	<ul> <li>Inquiries to the Medical Information Department: 57,488 (including telephone, e-mail and fax inquiries)</li> <li>Product Research Department: Published research papers: 26 (2017-2018) Presentations at scientific conferences: 18 overseas, 24 in Japan (2017-2018) Academic conference awards: 2 in Japan (2017-2018)</li> </ul>	HR • C h Productivity • E o

1. Copyright © 2018 IQVIA. Source: JPM 2017. Reprinted with permission. The scope of the market is defined by Chugai

2. Based on a survey of overall assessments of companies by physicians in hospitals with 100 or more beds, as defined by Chugai

#### SG initiatives in each division

Fostered employee awareness of energy saving through energy visualization Continued joint cleanup activities with a local high school for the Shinkawa River, which flows through the Kamakura Research Laboratories site

Conducted activities at Kamakura Research Laboratories to raise awareness of the mportance of cancer screening

As part of the Company's support for recovery from the Great East Japan Earthquake, held a charity sale at the Kamakura Research Laboratories of specialty products from the affected area

Fostered a corporate culture where employees can participate actively after returning from childcare or other leave

Held cross-cultural training to cultivate leaders who can succeed globally Held study sessions with instructors from other industries to promote global success

Created a new operating model that makes greater use of the Roche system Raised productivity and transformed mindsets by promoting improvement activities

Reduced greenhouse gas emissions with the scheduled introduction of highefficiency air conditioning

Promoted reduction of energy consumption through an energy visualization task force

Conducted firefighting activities in cooperation with local fire departments

Promoted "Techno" technology review activities to create new core competencies and strengthen basic technologies

Held U-MAST (at Utsunomiya Plant), UK-NEXT (at Ukima Plant) and F-OPEX (at Fujieda Plant) as initiatives to train young employees through proposal and mprovement activities

Held interdivisional exchange meetings (Knowledge Cube for Marketing & Sales, Medical Affairs and Pharmaceutical Technology divisions and BRIDGE for Research, Clinical Development, Translational Clinical Research and Pharmaceutical Technology divisions)

Held Lean Activity Leader activities at the three plants, the research departments and the Quality Assurance Dept.

Conducted Bilateral actions of Business and Quality (BBQ) initiatives

ntroduced eco-friendly cars in MR fleet

Promoted paperless operations in areas such as meeting materials

Promoted proper use of medicines through support for improvements in the rate and accuracy of testing

Participated in Lung Cancer Awareness and attended to patient requests regarding drugs Promoted disease awareness through cooperation with businesses in other industries

Held the Bone and Joint Forum nine times during the year as a measure against ocomotive syndrome

Produced and disseminated videos for disease awareness and promotion of adherence to treatment

Disseminated information on a new issue related to cancer treatment (cancer patient dementia) through the Company website

Produced "A Day in the Life of a Primary Care Pharmacist," a video to promote wider recognition of primary care pharmacists

Promoted disease awareness via FM radio

Held Innovation Club meetings to discuss cross-divisional proposals

Conducted a training program from the standpoint of training global medical numan resources

Established a global collaboration team to promote visualization of operations at overseas subsidiaries

Environment Environmental Protection Society Providing Value to Society HR Human Resources Productivity Raising Productivity

Items	Main initiatives	Main performance indicators in 2017		Examples of E
Drug Safety	<ul> <li>Strengthening pharmacovigilance system to meet the world's strictest standards and most comprehensive global regulations</li> <li>Providing solutions to patients and healthcare professionals using drug safety information</li> <li>Preparing and implementing risk management plans (RMPs)</li> </ul>	<ul> <li>Cases for which safety information was collected from Japan and overseas according to global standards for clinical trials and post-marketing studies: 136,151 (January - December 2017)</li> <li>Increased capacity for generating safety information using advanced technologies such as epidemiology and information technology, and established the new specialist position of Safety Expert for handling safety information (April 2017)</li> </ul>	<ul> <li>RMPs prepared and carried out for thorough risk management: 12 products (as of February 2018)</li> <li>Papers and conference presentations on safety based on the results of post-marketing surveillance: 20 (2017)</li> </ul>	Environment • F Society • F • F • ( Productivity • ( • ( • ( • (
Intellectual Property	<ul> <li>Protecting and effectively using rights for broadly applicable innovative technologies</li> <li>Filing high-quality patent applications and effectively allocating resources</li> <li>Aggressively filing patent applications outside Japan with a view to global co-development</li> </ul>	<ul> <li>Patents held (including pending applications): 4,219</li> <li>New patents granted worldwide: 188</li> <li>Defended the market for Oxarol Ointment with a patent-infringement lawsuit against manufacturers of generics</li> </ul>	<ul> <li>Operated a system for monitoring other companies' patents</li> <li>Enhanced cooperation with the Pharmaceutical Technology Division in ways such as expanding the scope of meetings to review intellectual property</li> </ul>	Environment • F C HR •    F Productivity • (
ltems	Main initiatives	Main performance indicators in 2017		Items describe
Environment, Health and Safety	<ul> <li>Promoting global warming countermeasures, resource conservation and waste reduction</li> <li>Thoroughly managing chemical substances</li> <li>Disclosing environmental information</li> <li>Enhancing environmental awareness and making environment- related contributions to local communities</li> <li>Creating safe, comfortable workplaces</li> </ul>	<ul> <li>Energy consumption per employee compared with 2010: -16.6% (Chugai Group in Japan)</li> <li>Recycling ratio in 2017: 76.4% (Chugai Group in Japan)</li> <li>Final disposal ratio in 2017: 0.8% (Chugai Group in Japan)</li> <li>Ratio of eco-friendly cars: 78.1%</li> </ul>	<ul> <li>Certified as a White 500 company</li> <li>Occupational accident incidence rate: 1.52 (No. of occupational accidents resulting in illness, injury or death / No. of hours actually worked x 1,000,000)</li> <li>Occupational accident severity rate: 0.006 (No. of workdays lost / No. of hours actually worked x 1,000)</li> </ul>	Environmental Prot Activities/Climate ( Prevention of Air, V Performance Data
Social Contribution	<ul> <li>Creating an inclusive society through support for para-sports</li> <li>Nurturing the next generation who will carry science and technology forward</li> <li>Supporting employee volunteer activities</li> <li>Contributing to communities where Chugai Group facilities and sites are located</li> </ul>	<ul> <li>Conducted awareness-raising and support activities for para-sports (served as title sponsor of a wheelchair softball tournament, provided training facilities, and operated a booth for experiencing wheelchair tennis and chair skiing)</li> <li>Donation of welfare vehicles to provide transportation for home welfare services: Total of 248 vehicles over 33 years (1 vehicle each to 5 organizations in 2017)</li> <li>Cumulative number of countries receiving free therapeutic drugs for treating lymphangiomas: more than 80 (program in its 27th year)</li> </ul>	<ul> <li>Number of locations in which Chugai employees participated in the 24-hour charity event Relay For Life Japan: 29</li> <li>Biology lab classes for children at the Japan Science Foundation's Science Museum: 110 participants in 12 labs</li> <li>Endowed courses at Waseda University: 2</li> <li>Number of employees who took volunteer leave: 48</li> <li>Participated in Pink Ribbon activities</li> </ul>	Relay for Life Japa Chugai's Social Cor (Japanese only)
Corporate Communication	<ul> <li>Proactively disclosing information and promotion of IR activities for institutional investors, security analysts, individual investors and other stakeholders in Japan and overseas</li> <li>Building good relationships with media outlets and disseminating information appropriately and in a timely manner (media relations)</li> <li>Promoting global communications to enhance global dissemination of information and to improve the crisis preparedness of the Chugai Group</li> <li>Building and establishing the corporate brand</li> <li>Information and establishing the corporate brand</li> &lt;</ul>		<ul> <li>Branding campaign (TV commercials and newspaper advertisements)</li> <li>Won Grand Prize at 19th Nikkei Annual Report Awards</li> <li>Won 3rd Prize at 2017 Excellence in Corporate Disclosure Selection in the pharmaceuticals category</li> <li>Won Prize for Best Work in the cosmetics/pharmaceuticals/fashion/ daily commodities category at the 85th Mainichi Advertisement Design Competition held by the Mainichi Newspapers Co., Ltd.</li> </ul>	Shareholder Inform Individual Investors
Corporate Governance	<ul> <li>Prompt decision-making, clarification of executive responsibilities and management transparency</li> <li>Enhancing decision-making by introducing outside perspectives</li> <li>Maintaining an internal control system</li> <li>Promoting compliance with the Pharmaceuticals and Medical Devices Law, fair competition codes, promotion codes, and other laws and regulations</li> </ul>	<ul> <li>Board of Directors meetings: 9 (average attendance rate of outside directors 100%)</li> <li>Auditing system: 4 Audit &amp; Supervisory Board members (including 2 outside members)</li> </ul>	<ul> <li>Convened the Chugai International Council (CIC)</li> <li>Number of Compliance Committee meetings: 4</li> <li>Number of Corporate Social Responsibility Committee meetings: 2</li> </ul>	Basic Corporate Go Internal Control Sys Guidelines/Emerge
Human Resources	<ul> <li>Fostering human resources who are competent in the global arena</li> <li>Building work environments in which diverse people can succeed</li> <li>Building sound labor-management relations</li> <li>Fostering high ethical standards through training on the Chugai Business Conduct Guidelines (Chugai BCG); making continuous efforts to build human rights awareness</li> </ul>	<ul> <li>Implemented leader development program, all-employee program, division programs and Self-Innovation Program (SIP)</li> <li>Number of employees posted through the Roche Human Resource Exchange Program: 164 (2004-2017)</li> <li>Percentage of female managers:<sup>3</sup> 12.5%</li> <li>Percentage of employees using the telecommuting system:<sup>4</sup> Male 13.0%, Female 29.7%</li> <li>Percentage of employees taking childcare leave: Male 52.0%, Female 98.8%</li> </ul>	<ul> <li>Percentage of employees with disabilities: 2.17%</li> <li>BCG and human rights training attendees: 13,856 (includes repeat attendees; Chugai Group in Japan)</li> <li>Conducted compliance surveys for employees in Japan and overseas: 6,595 participants (6,131 in Japan, 464 outside Japan)</li> <li>Selected as a Nadeshiko Brand in March 2018 by the Ministry of Economy, Trade and Industry and the Tokyo Stock Exchange</li> <li>Selected as one of the New Diversity Management Selection 100 companies in March 2018 by the Ministry of Economy, Trade and Industry</li> </ul>	Business Conduct ( Aptitude/Personnel Environments/Putti Initiatives/Diversity Employees/Facilita

3. Number of female managers as a percentage of the total number of managers in the Company (non-consolidated)

4. Percentage of eligible employees who used the system

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SG initiatives in each	division		

- Promoted paperless operations for stored materials and meeting materials
- Held awareness-raising activities for the media to disseminate accurate medical information Provided the latest drug safety information through lectures for healthcare providers Contributed to the enhancement of Japan's epidemiological database
- Used information and communications technology (ICT) to construct a system for timely provision of the safety information doctors need
- Cut back on processes and paper use through the introduction of an image sharing system Dutsourced the management of post-marketing surveillance and individual adverse drug reaction data
- Formulated a paperless scheme for internal management of applications for public disclosure approval
- Implemented measures to facilitate direct communication with overseas law firms for batent applications outside Japan
- Confirmed the effectiveness of concentrating overseas agents to reduce costs

#### ed in detail on website (As of March 31, 2018)

tection, Safety and Health/Mid-Term Environmental Goals/Safety and Health Change Countermeasures/Chemical Substance Management/Waste and Recycling/ Water and Soil Pollution/ Education, Communication and Environmental Accounting/

n/NPO Shuhei Ogita Fund Supporting Patients with Lymphatic Malformations/ ntribution Activities/Efforts for Society (Japanese Only) Support for Para-Sports

nation/Shareholder Meetings/Shareholder Returns/Financial Results/Message to s (Japanese only)/Chugai Brand Story/Videos & Advertisements

overnance Policy/Corporate Governance Report/The Resolutions concerning the stem by the Board of Directors/Relationship with Roche/Chugai's Transparency ency Response

Guidelines/Talent Management According to Each Person's Capabilities and el Systems That Help Our Diverse People to Succeed/Creating Supportive Work ing the Chugai BCG into Practice at a Personal Level/Diversity and Inclusion y and Inclusion Promotion System/Initiatives to Promote the Success of Diverse ating Work-Life Balance/Performance Data Related to Diversity and Inclusion

### Research

#### Initiatives and Performance in 2017

13 In-house products in pipeline (As of February 1, 2018)

# 61

Academic papers and presentations at scientific conferences regarding Chugai's innovative proprietary technologies (2013-2017)

# 97

Published academic papers regarding Chugai's research findings (2013-2017)

#### Features of Our Research **Functions**

Chugai began conducting research and development of biopharmaceuticals more than 30 years ago, and the former Nippon Roche had also established world-class technology for the discovery of chemically synthesized agents. Over the years, we have cultivated knowledge and gained experience through our own pioneering initiatives while also incorporating outside technologies. As a result, we have continuously evolved our technologies, and have built a technology platform that we can flexibly and appropriately apply to drug discovery.

We are using this platform to generate a steady stream of innovative new drugs with first-in-class or best-in-class potential to address unmet medical need. In addition to developing antibody engineering technologies ahead of other companies, Chugai has industry-leading research and technological capabilities backed by small and middle molecule<sup>1</sup> technologies, the world-class research infrastructure of the Roche Group and a powerful external network with academia and other parties. Through presentations of research findings at scientific conferences and other means, these strengths lead to benefits for the medical community around the world, as well as the creation of in-house projects.

1. Middle molecules have significant potential because they are capable of inhibiting protein-protein interaction (PPI) in intercellular molecules, which is difficult to achieve with antibodies and small molecules.

#### Allocation of Research Resources

In allocating research resources, we prioritize each project based on the following criteria:

- The project's potential for development as a novel medicine that can be clearly differentiated
- Whether it has a scientific basis for addressing unmet medical need
- Whether it will enable personalized healthcare (PHC)

At various decision points during research, we focus first and foremost on patient need, reflecting our belief that creating medicines truly needed by patients and healthcare providers will lead to Chugai's medium-to-long-term growth.

#### **Recent Research Activities**

In 2017, PHC-based projects represented 51 percent of our total pipeline, including projects in-licensed from Roche.

We have also achieved significant results in development of proprietary antibody engineering technologies.<sup>2</sup> In May 2014, we licensed these technologies to Roche, including the Recycling Antibody<sup>®</sup>, which extends a therapeutic antibody's duration of efficacy, the Sweeping Antibody®, which can eliminate disease-causing antigens from plasma, and the bispecific antibody. In November 2017, Hemlibra obtained approval in the United States for the treatment of hemophilia A. This was the first approval for a project in which our proprietary

(January 1, 2017 - February 1, 2018)

**Progress of Development Projects** 

	Number of Projects	Breakdown		
		New Molecular Entities	Additional Indications	Additional Dosage and Administration/ Formulations
Approved	13	4	6	3
Filed	8	5	3	0
Started phase III	9	6	3	0
Started phase II	1	1	0	0
Started phase I	5	5	0	0
Development suspended	3	_	_	_

#### antibody engineering technologies were applied. We have also filed applications in Europe and Japan and are aiming to obtain approval in both markets in 2018.<sup>3</sup>

In April 2017, a collaborative lab began operating under our comprehensive agreement with Osaka University Immunology Frontier Research Center (IFReC). Immunity is involved not only in diseases of the immune system itself, but also in cancer and various other diseases. and immune-mediated therapies are now becoming mainstream cancer treatments.

Combining the global top-class research in immunology at IFReC and Chugai's expertise in drug discovery research, accumulated through its proprietary technologies, is expected to result in the creation of innovative new drugs.

Research at satellite labs has also yielded solid results, leading to the successful establishment of stable cell lines of colon cancer stem cells in October 2012. In addition, URC102, a small molecule compound discovered at C&C Research Laboratories in South Korea, has advanced into clinical development, and new drug targets have also been identified at Forerunner Pharma Research Co., Ltd. Moreover, Chugai Pharmabody Research Pte. Ltd. (CPR), which we established in Singapore in 2012, is making steady progress in research focusing on discovery of new therapeutic antibodies. SKY59, a project that originated at CPR, also entered clinical development in 2016.

2 For details on Chugai's proprietary antibody engineering technologies, see our website. (https://www.chugai-pharm.co.jp/english/profile/rd/ index.html).

3. Approved in Europe in February 2018

#### **Bioethics in R&D**

To ensure that research using human-derived test material is carried out appropriately, Chugai has established Ethical Guidelines for Research That Uses Human-Derived Test Material and a Research Ethics Committee. More than half of the members of this committee are from outside the Company,

enabling fair evaluations from a pluralistic frame of reference. Moreover, we strive to ensure that research is conducted with respect for human rights by offering guidance to our researchers on the necessary ethical knowledge and standards required when conducting research on human-derived test material, including the Declaration of Helsinki and protection of personal information.

#### **Our View of Animal Welfare**

When handling laboratory animals used in research, Chugai acts in accordance with the Guidelines for the Care and Use of Laboratory Animals it has established to respect their lives from the standpoint of animal welfare, and to minimize their pain, keeping in mind the scientific conditions.

Based on the principles of the 3Rs (Replacement, Reduction and Refinement), the Institutional Animal Care and Use Committee has added an examiner from outside the Company to assess the validity of research using laboratory animals from a more objective viewpoint and to make appropriate improvements to reflect changes in the social environment and

scientific progress. At the same time, an institutional gualification program was adopted for researchers and animal handlers to cultivate concern for animal welfare through education and training. These measures were positively evaluated by AAALAC International,<sup>4</sup> a global independent evaluation organization, and Chugai has maintained full accreditation since 2007.

4. Association for Assessment and Accreditation of Laboratory Animal Care International, a private nonprofit organization that promotes the humane treatment of animals in scientific research through voluntary inspection and accreditation programs. More than 900 facilities in 39 countries have been accredited.

#### **Comparison of Drug Discovery Modalities**

	Small molecules	Middle molecules	Biologics
Molecular weight	Below 500	500 - 2,000	10,000 and above
Target specificity	Fair	High	High
Intracellular targets	Wide range	Numerous	Limited
PPI inhibition	Fair	Good	Good
Administration route	Oral/Injection	Oral/Injection	Injection
Manufacturing method	Organic synthesis	Organic synthesis	Cell culture

### Considering a Future of Healthcare That Is Shaped by the Fusion of Science and Technology

Rapid scientific and technological advances, especially in life science and information and communications technology (ICT), are bringing dramatic changes to society and the pharmaceutical industry. Chugai's Science and Technology Intelligence (STI) Department was established in April 2017 as an intelligence unit to consider Chugai's response to emerging issues in the healthcare business.

Healthcare in the future is expected to center on PHC, which provides optimal solutions tailored to individual patients, and in addition to diagnosis and treatment, which are the focus of the current model, greater value will need to be provided in areas such as prevention and prognosis. Our goal is to contribute to higher-quality healthcare with solutions that lead to new value, and a critical part of that effort is formulating strategies for disruptive innovation,\* which will be essential for realizing such solutions.

#### STI's mission is to find promising leads for pursuing disruptive innovation, and to create strategies for bringing it about. STI will perform radar, hub and intelligence functions in cooperation with internal crossfunctional teams of experts in the three areas of life science, healthcare ICT, and data utilization. A number of projects have already begun

#### Scope of STI

#### Life Science Improvement of the **Current Medical Paradigm** New treatment modalities utilizing cells and nucleic acids

#### **Drug Discovery Modalities**

In the pharmaceutical industry, modality refers to the material classification of drugs such as therapeutic antibodies or therapeutic nucleic acids. Until the 1990s, small molecule drugs were virtually the only modality available, but modality options are now increasing. Chugai is currently focusing on establishing middle molecules as a third modality in addition to biologics and small molecules, in which it is already strong.

Concrete results have yet to emerge, but we will focus on this new initiative to generate innovation ahead of other companies.

\* Innovation that disrupts the order of existing business and causes drastic changes in the industry structure.



### Development

#### Initiatives and Performance in 2017

Pipeline projects (As of February 1, 2018)

New products launched and new indications (2013-2017)

clinical studies

the industry.

#### **Our Development Functions**

To bring innovative pharmaceuticals to patients as quickly as possible, Chugai has established a lifecycle management\* system for project-level integrated management of research, regulatory affairs, drug safety, manufacturing and other functions, and cooperates with numerous medical institutions and clinical research centers. In this way, we work to implement clinical trials distinguished by exceptional speed, efficiency and scientific rigor.

Specifically, in clinical development, we draw up clinical development plans based on the latest scientific findings and invite medical institutions to conduct clinical trials. In manufacturing, we examine commercial production that will turn candidate compounds into pharmaceutical products and manufacture investigational drugs for clinical trials. In drug safety, we ensure a high level of safety in clinical trials by gaining an understanding and beginning assessments of each drug's safety profile from the early stages.

To promote global development, in April 2018 Chugai integrated the clinical study management functions of the Translational Clinical Research (TCR), Clinical Development and the Medical Affairs divisions into the Clinical Development Division. Through this new configuration, Chugai will enhance cooperation among its operations in Japan, the United States and Europe, deepen cooperation with Roche, including the

development projects from in-house research, and guickly move them into global development. TCR is Chugai's first global division in charge of TCR functions in Japan,

#### Projected Submissions (Post-PoC NMEs and Products)



1. New molecular entity 2. Renal cell carcinoma 3. Non-small cell lung cancer 4. Small cell lung cancer 5. Muscle invasive urothelial carcinoma 6. Diffuse large B-cell lymphoma 7. Under development for the indication of atopic dermatitis by licensees [Galderma S.A. (overseas) and Maruho Co., Ltd. (Japan)] 8. Idiopathic pulmonary fibrosis

### **Proprietary Technologies**

Drug discovery technologies, largely antibody engineering technologies, are Chugai's core competence. We are focused on development of proprietary technologies that are necessary for addressing areas of unmet medical need. Their application leads to the generation of innovative and competitive medicines.

Chugai's research and development operations have used our groundbreaking advances in research techniques to develop a series of technologies that overturned conventional wisdom about antibody engineering. Examples include the development of our Sweeping Antibody®, Recycling Antibody® and bispecific antibody technologies. In addition to antibody engineering and small molecules, we have selected drug discovery technologies for middle molecules as a candidate for our next-generation core technology. We intend to concentrate investments in this area to establish this new technology and quickly generate new projects.

#### **ERY974 and Use of Bispecific Antibody Technology**

Unlike normal antibodies, a bispecific antibody can bind simultaneously to two different target molecules. Due to their complex structure, it was extremely difficult to manufacture bispecific antibodies with high levels of purity and efficiency. However, commercial production became possible with Chugai's proprietary ART- Ig\* technology. Not only do bispecific antibodies provide the effect of two agents in one, but flexible approaches to applying their special features will make them key in creating previously unachievable new therapies to address unmet medical need.

ERY974, an anti-tumor agent currently undergoing an overseas phase I clinical study, is the second project from Chugai research to apply ART-Ig bispecific antibody technology following Hemlibra, which received approval in the United States and in Europe as a treatment for hemophilia A with inhibitors for blood coagulation factor VIII. ERY974 is a T-cell redirecting antibody (TRAB). By simultaneously binding to specific proteins expressed on T cells, which are

immunocytes, and on cancer cells, TRAB is expected to direct T cells to cancer cells and also activate T cells, specifically damaging neighboring cancer cells. Compared with immunecell therapy displaying the same mechanism of action, TRAB does not require removal of T cells from the patient's body for treatment, and thus is expected to offer an advantage as a therapeutic antibody that can be provided uniformly and stably at a lower cost.

ERY974 Mechanism of Action **Bispecific Antibody** Light Light chain

\* For details on Chugai's proprietary antibody engineering technologies, see our website. (https://www.chugai-pharm.co.ip/english/profile/rd/ technologies.html)

#### SKY59 and Application of Recycling Antibody® Technology

Chugai's proprietary Recycling Antibody® is an antibody engineering technology that enables efficacy to be maintained for a longer duration than that of conventional antibodies due to improved pharmacokinetics and a prolonged half-life. Normally, an antibody remains bound to an antigen, but a Recycling Antibody® is designed to bind to antigens multiple times. Because it has been engineered to be pH-dependent, the antibody separates from the antigen in the cell and only the antibody is recycled to plasma. The use of Recycling Antibody® technology is expected to produce an effect at an extended dosing interval and low dosage. This technology was first applied to satralizumab (SA237), which is in a phase III multinational study as a potential treatment for neuromyelitis optica, and prolonged plasma half-life has been demonstrated in clinical trials.

SKY59 is the second project to apply Recycling Antibody® technology. It targets the C5 complement component, and a phase I/II multinational study as a potential treatment for paroxysmal nocturnal hemoglobinuria is under way. It was the first project to move into clinical development among those created and

developed from the early stages by Chugai Pharmabody Research Pte. Ltd., which was established in 2012. Although C5 complement is highly present in plasma, Recycling Antibody® technology makes it possible to use fewer antibodies to capture C5 molecules compared with conventional antibodies. The therapeutic antibody currently in use is administered as a continuous intravenous infusion, which requires regular hospital visits. Offering a self-injectable formulation for subcutaneous administration with reduced dosing frequency is expected to improve patient quality of life. Focusing on this benefit, Chugai and Roche began joint development from an early stage.



PHC-based development projects (As of February 1, 2018)

15 Products in-licensed from Roche (2013-2017)

promotion of the rapid development of Chugai products, and build a flexible framework for formulating and conducting

Through our alliance with the Roche Group, we are implementing multiple global development projects (multinational studies) and strengthening the process to enable simultaneous development of drugs and companion diagnostics suitable for personalized healthcare (PHC). Through these initiatives, we are creating best practices in development and filing for approval in Japan. which may contribute to the advancement of

\* The various measures taken to maximize the potential value of a drug, including shortening development time, expanding sales, extending the product's life, and conducting appropriate cost control. Competitiveness can be strengthened further by using earnings from sales of established drugs to strategically reinvest in new drug development, marketing or other areas.

#### **Our Translational Clinical Research Functions**

The TCR Division was established in 2015 to specialize in early clinical development and bolster its functions with the aim of rapidly acquiring proof of concept (PoC) for

- the United States and Europe.

For promising products from Chugai research, Chugai uses the screening functions of its U.S. subsidiary Chugai Pharma USA to conduct thorough disease target identification from the exploratory research stage in order to set the direction for development. We are thus concentrating on the development plans most likely to maximize the value of in-house projects and obtain early PoC.

As measures to enhance the functions of TCR in clinical pharmacology we are working diligently to improve the accuracy of clinical pharmacokinetics and prediction of clinical efficacy, and also to discover biomarkers for confirming efficacy and selecting appropriate patients. In 2017, we deepened exchanges with members in research and early clinical development at Roche and Genentech to promote common platforms and more efficient use of resources for clinical pharmacology in the Roche Group.

#### Results and Overview of **Development Activities**

Of the 41 projects currently in Chugai's pipeline, 13 originated from Chugai research, and half are based on PHC (as of February 1, 2018). In 2017, all projects made steady progress. Chugai filed for regulatory approval for eight projects, and obtained approval for 13 projects. Chugai's pipeline grew even richer, with five new projects in-licensed from Roche advancing to the clinical phase.

	<b>Tecentriq</b> (RG7446) Ovarian cancer	polatuzumab vedotin (RG7596) DLBCL <sup>6</sup>	<b>nemolizumab</b> (CIM331) <sup>7</sup> Pruritus in dialysis Patients
	<b>Tecentriq</b>	<b>ipatasertib</b>	<b>lebrikizumab</b>
	(RG7446)	(RG7440)	(RG3637)
	RCC (adjuvant)	Breast cancer	IPF <sup>8</sup>
<b>nab</b>	<b>Tecentriq</b>	<b>ipatasertib</b>	<b>RG6206</b>
5168)	(RG7446)	(RG7440)	Duchenne muscular
itis optica	MIUC <sup>5</sup> (adjuvant)	Prostate cancer	dystrophy
NRD101) arthritis/ eriarthritis	<b>Tecentriq</b> (RG7446) Urothelial carcinoma	Kadcyla (RG3502) Breast cancer (adjuvant)	<b>crenezumab</b> (RG7412) Alzheimer's disease
	<b>Tecentriq</b>	Tecentriq	<b>gantenerumab</b>
	(RG7446)	(RG7446)	(RG1450)
	NSCLC (adjuvant)	Prostate cancer	Alzheimer's disease
019		2020 and beyond	

20

### Production

#### Initiatives and Performance in 2017

Invested in facilities to handle multiple antibody development projects simultaneously (For details on capital investments,

see "Capital Investments" on page 102.)

#### Created and started operation of a world-class system for pharmaceutical quality management

#### **Our Production Functions**

Our production functions play a wide range of roles in the pharmaceutical value chain from turning drug candidates into products to stably supplying them. These candidates may be compounds created in our laboratories or projects in-licensed from Roche or elsewhere. Product creation includes research on commercialization of the biological and small molecule active pharmaceutical ingredients (APIs) used as active ingredients, the design and study of commercialization of formulations and packaging for the products that will ultimately be used by patients, and the summarizing of data collected during the manufacturing and development of investigational drugs used in clinical trials in order to prepare application materials.

Through product creation, Chugai works to provide previously unavailable pharmaceuticals to patients as quickly as possible.

However, our production functions do not stop at simply creating products. They are responsible for maintaining the trust of patients and healthcare providers by ensuring a stable supply of all products - a duty central to Chugai's existence as a pharmaceutical manufacturer. That is why we need to build and maintain both manufacturing capabilities that reliably generate high-guality products and a robust supply chain that connects manufacturing sites and markets inside and outside Japan, including with Roche.

Chugai already has competencies at Japan's top level in several respects, including bioproduction technology and the ability to accommodate inspections. We will leverage

#### **Overview of Production Bases**

Plant	Features	Products Manufactured
Utsunomiya Plant (Tochigi Prefecture)	One of Japan's largest facilities for cultivating biological active pharmaceutical ingredients (APIs) and a state-of-the-art production line for injectable formulations	Biological APIs: Actemra APIs Injectable formulations: Actemra, Epogin and others
Ukima Plant (Tokyo)	Manufactures and packages solid and injectable formulations and biological APIs. Production base for investigational biologics.	Biological APIs: Epogin APIs and others Injectable formulations: Oxarol and others
Fujieda Plant (Shizuoka Prefecture)	Integrated production system from API synthesis to formulation and packaging. Production base for investigational API synthesis.	API synthesis: Edirol APIs and others Solid formulations: Edirol, Tarceva, Xeloda and others

our strengths as a member of the Roche Group to continue working to become a top pharmaceutical company with more powerful functions for product creation and stable supply.

#### Reliable Distribution of Pharmaceuticals and Stable Procurement

In addition to the three Chugai Group plants in Utsunomiya, Ukima and Fujieda, Japan, we have production bases (including contract manufacturing organizations) in various regions around the world. We have also created a rigorous quality control system in line with global standards, including compliance with GMP.\*

Raw material procurement is key in providing a stable and continuous supply of high-quality pharmaceuticals to healthcare providers and patients. However, the stable procurement of raw materials is constantly exposed to risks such as discontinued production due to the merger or closing of suppliers, spikes in prices or problems with availability due to fluctuations in the balance of supply and demand, or delays in delivery caused by accidents at suppliers. To minimize these risks and maintain a stable supply of raw materials we promote the globalization of our suppliers of raw materials and intermediate products in tandem with the globalization of our production bases for finished products. Our production functions ensure shipping quality between bases, and we adopt various risk countermeasures such as increasing the number of locations that produce essential products, based on our experience from the

Great East Japan Earthquake. Through these and other measures to strengthen supply chain management as it becomes increasingly complex and global, we are working to maintain and improve the reliability of distribution in Japan and overseas.

**69** 

Published research papers from the

Pharmaceutical Technology Division

(2013-2017)

Our subsidiary Chugai Distribution Co., Ltd. handles distribution of pharmaceuticals in Japan. The company's computerized inventory management and inspection ensure stable and safe distribution, and the staff employs original methods for the careful packaging of products to enable easy sorting and prevent damage when recipients open the cartons. \* Good Manufacturing Practice: Standards for pharmaceutical production management and quality control

#### Quality Assurance Approach and System

Chugai always puts the patient first as it strives to provide high-quality products and services that offer outstanding safety and efficacy. To this end, our quality assurance operations work to improve product quality by cooperating closely with manufacturing sites, including Roche's.

Quality assurance functions have diversified in recent years in response to the increasing complexity of the product supply process and the acceleration of development with the introduction of the fast-track review system to support the early launch of innovative new drugs. Quality requirements are becoming increasingly stringent with Japan's accession to the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) in July 2014 and the start of implementation of the international Pharmaceutical Quality System guideline.

In view of these trends, Chugai conducts consistent GMP throughout the product lifecycle from development to manufacturing, and is working to further strengthen oversight of GMP management to promote more rigorous and high-level quality assurance. As part of these efforts, Chugai has created and operates a world-class system for pharmaceutical quality management.

# Marketing

#### Initiatives and Performance in 2017

27.3%1 Share of sales in the Japanese therapeutic antibody market (2017)

20.2%1 Share of sales in the

Japanese oncology market (2017)

1. Copyright © 2018 IQVIA. Source: JPM 2017. Reprinted with permission. The scope of the market is defined by Chugai. 2. Based on survey of overall assessments of MRs by physicians selected according to terms defined by Chugai.

#### Oncology

#### Sales (Billions of Yen)

2016	92.1	34.1	
2017	① 93.1	② 33.6	

1. Included in Others from 2017

1)	Avastin	Launch in Japan: Jun. 2007
2)	Herceptin	Launch in Japan: Jun. 2001
3)	Rituxan	Launch in Japan: Sep. 2001
411	Alecensa	Launch in Japan: Sep. 2014
5)	Perjeta	Launch in Japan: Sep. 2013
6)	Xeloda	Launch in Japan: Jun. 2003
7)	Tarceva	Launch in Japan: Dec. 2007
8)	Kadcyla	Launch in Japan: Apr. 2014
9	Zelboraf	Launch in Japan: Feb. 2015
012	Neutrogin	Launch in Japan: Dec. 1991
3	Akynzeo	Launch in U.K.: Sep. 2015 Launch in Ireland: Dec. 2015
4	Aloxi	Launch in U.K.: Jan. 2015

#### Review of 2017 Performance and 2018 Outlook

In 2017, sales in the oncology area in Japan increased ¥5.6 billion, or 2.5 percent, year on year to ¥225.9 billion. Sales of new product Alecensa continued to grow substantially with an increase in use as a first-line treatment and a high rate of adherence. With the advent of the new therapeutic category of cancer immunotherapy, the position of Avastin in treatment is changing, and it is maintaining a level of sales as a mainstay drug in the area of oncology. Perjeta and Rituxan also contributed to sales growth. Sales of Alecensa outside Japan including exports to Roche increased a substantial ¥10.2 billion, or 276 percent, to

### Bone and Joint Diseases

#### Sales (Billions of ven) 30.2 26.7 9.3 7.3 3 22 9.4 2016 (3) (4) 8.8 8.7 2017 33.1 29.6

2. Included in Others from 2017

)6	Actemra	Launch in Japan: Jun. 2005
	Edirol	Launch in Japan: Apr. 2011
)	Suvenyl	Launch in Japan: Aug. 2000
D	Bonviva	Launch in Japan: Aug. 2013
5)	Alfarol	Launch in Japan: Jan. 1981

#### Review of 2017 Performance and 2018 Outlook

In 2017, sales in the bone and joint diseases area in Japan increased ¥7.2 billion, or 8.4 percent, year on year to ¥93.3 billion. In addition to growth from uptake of Actemra as a first-line biologic, sales growth continued for Edirol, which has been recognized as a base treatment for osteoporosis, and for Bonviva, which was launched in an oral formulation in April 2016 in addition to the intravenous formulation. Sales of Actemra outside Japan including exports to Roche

#### **No.** 1<sup>2</sup> Satisfaction ranking for Actemra in the RA market<sup>2</sup> (2017)

36 Number of branch offices in the new area-based system for providing solutions (As of April 2017)



¥13.9 billion, supported by regulatory approval in Europe and centered on the United States, where Alecensa's use is expanding as a second-line treatment.

In 2018, sales are expected to decrease significantly due to the scheduled return of the premiums for new drug creation for Herceptin and Rituxan, among other factors. On the other hand, we forecast growth from further uptake of Alecensa as a first-line treatment, as well as from the photodynamic diagnostic agent Alaglio, which is a new product, and Tecentriq, an anti-PD-L1 monoclonal antibody that obtained approval in January 2018. We aim to maintain Avastin's position as a treatment for multiple types of cancer.



increased ¥0.6 billion, or 1.0 percent, to ¥60.9 billion as firm global sales by Roche compensated for the negative effect of exchange rates.

In 2018, we expect continued firm sales of treatments for rheumatoid arthritis (RA) and osteoporosis in Japan. Outside Japan, we expect double-digit growth or higher in sales of Actemra, mainly due to further uptake of the subcutaneous formulation for RA and sales for giant cell arteritis, which became an additional indication in 2017.

# Medical Affairs

#### Initiatives and Performance in 2017

25 Contract-based post-marketing studies (including 17 in accordance with ICH-GCP guidelines) (As of January 31, 2018)

### 153 Staff with GCP Passport (JSCTR certification)

#### **Our Medical Affairs Functions**

innovative drugs, Chugai recognizes the importance of ensuring that the value of its products is delivered accurately to patients. which will lead to better treatment. We have been focusing on generating scientific data in support of this objective and supplying appropriate information to healthcare providers.

Moreover, we maintain global-level compliance standards, including funding and medical affairs<sup>1</sup>. At the same time, we are working to further enhance our internal systems to help raise the quality and scientific level of clinical and preclinical our operating environment.

Since 2012, Chugai has unified functions for medical affairs and promotion of preclinical studies by setting up the Medical Affairs Division to establish the independence of all functions related to medical science. Medical staff was also dispatched to each area to set up a framework for consistent promotion of medical affairs throughout the Company. The Medical Affairs Division was then restructured to strengthen organizational governance and

Concurrently, we began operation of a scheme for contract-based post-marketing studies (see the column at right for details) to guarantee the independence and transparency of research. We promptly set up a structure for responding to Ethical Guidelines on Medical Research Involving Human Subjects, which were enforced from April 2015. At the same time, to raise the quality and reliability of research, we established a research support structure that conforms to the GCP<sup>2</sup> guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Moreover, we are building an organization to support global post-marketing studies based on these structures. We are also preparing an implementation and support system for post-

# (As of January 31, 2018)

overseas subsidiaries.

### In addition to creating a steady flow of

transparency and the separation of marketing (basic) research and to deal with changes in

#### **Strengthening Medical Affairs** Functions and Initiatives

compliance in these unified activities.

clinical studies in Japan.

### Chugai's Contract-Based Post-Marketing Study Framework Scope of clinical study responsibilities Parent body for study operations ared by everyone involved, including Chugai. operational support, but does not intervene in study results Contract :....**X**... Does not intervene in study results

<ul> <li>Responsibility is s</li> <li>Chugai can provid</li> </ul>	shi de
Contract (Work order)	dy
Chugai Pharmaceutical Co	

#### **Renal Diseases**



3 Included in Others from 2017

1 Mircera	Launch in Japan: Jul. 2011
2 Oxarol	Launch in Japan: Sep. 2000
3 Epogin	Launch in Japan: Apr. 1990

#### Review of 2017 Performance and 2018 Outlool

Sales in the renal diseases area in Japan in 2017 decreased ¥1.8 billion, or 4.4 percent, year on year to ¥39.3 billion. Mircera, which only needs to be administered once every four weeks, has established a reputation in the pre-dialysis segment for convenience and long duration of action, and use is expanding. However, sales decreased

biosimilars. Sales of Oxarol decreased partly due to the impact of generics. In 2018, we aim to maintain and improve the market presence of Mircera and Oxarol in

renal diseases

slightly due to competition including

the pre-dialysis and dialysis stages through

ongoing patient-centric activities rooted in

our high level of expertise in the area of

#### Others



4. Data for transplant, immunology and infectious diseases is included in Others from 2017.

1 Tamiflu	Launch in Japan: Feb. 2001
2 CellCept	Launch in Japan: Nov. 1999
3 Copegus	Launch in Japan: Mar. 2007
④ Pegasys	Launch in Japan: Dec. 2003
(5) Sigmart	Launch in Japan: Apr. 1984
6 Hemlibra	Launch in U.S.: Nov. 2017

#### **Review of 2017 Performance and** 2018 Outlook

In the influenza segment, where Chugai plays an important role as a provider of Tamiflu, we focus on providing information on the product's safety and effectiveness. including prevention of the disease, based on extensive clinical data accumulated over a long period. Sales of Tamiflu, including sales for government stockpiles, increased ¥3.4 billion, or 25.2 percent, year on year to ¥16.9 billion. Sales of CellCept, an immunosuppressant, increased ¥1.0 billion,

or 12.7 percent, to ¥8.9 billion due to increases in prescriptions accompanying kidney transplants and in use in treating lupus nephritis, a refractory disease for which it received approval in May 2016.

In 2018, we intend to continue proactively providing information on Tamiflu, centered on a wide range of facilities, by advancing e-promotion and cooperation with wholesalers. For CellCept, we will maintain our presence in the transplant segment and expect uptake for lupus nephritis.

Acquired third-party accreditation for MSL certification program from the Japanese Association of Pharmaceutical Medicine

Number of joint preclinical studies (As of January 31, 2018)

marketing studies under the Clinical Research Act that is scheduled to come into force in Japan in 2018. Furthermore, the Medical Information Department we established in 2016 responds to customer inquiries in a consistent fashion with appropriate information based on the latest science through collaboration with Roche and our

In 2017, Chugai acquired third-party accreditation<sup>3</sup> for its medical science liaison (MSL) certification program from the Japanese Association of Pharmaceutical Medicine. This accreditation means that the various activities of our MSLs in the area of medical affairs have been evaluated by an external institution. In the future, along with elucidation of the causes of diseases and pathological conditions, progress is expected in establishing preventive and treatment methods based on individual genetic, environmental and lifestyle differences. We will respond promptly to this changing environment by enhancing

our intelligence functions, such as using ICT and other means to obtain medical information and gain insights from its analysis, in order to focus on generating new data with higher scientific value and other activities that provide solutions. By disseminating appropriate information in ways such as these, we will contribute to patient-centric medical research in Japan.

- 1. Activities that contribute to healthcare from a scientific standpoint
- 2. Good Clinical Practice: Standards for conducting pharmaceutical clinical trials
- 3. Composed of evaluation criteria (a total of 222 items in 42 categories) from the three perspectives of independence from promotional activities (compliance system), medical and scientific expertise and the training system. In the accreditation examination, mail-in and on-site surveys of the evaluation criteria are conducted to evaluate whether the MSL certification program at the applicant company is being properly implemented.

#### **Contract-Based Post-Marketing Studies**

Raising transparency and addressing conflicts of interest in post-marketing studies have become key issues, reflecting society's growing interest in drug development after launch and scandals at pharmaceutical companies since 2013. Chugai has been operating its own post-marketing study scheme since 2012 under the name "contract-based post-marketing studies" to guarantee the independence and transparency of research. In our post-marketing studies, we ensure clear disclosure of research-related payments, relationships, conflicts of interest and other relevant matters. The data generated by these post-marketing studies have been highly evaluated at international conferences and has also been published in global guidelines.

We will continue working to validate new clinical data and disseminate even better information solutions to healthcare providers as we contribute to raising the level of

### Drug Safety

#### Initiatives and Performance in 2017

#### 136,151 Cases for which safety information was collected in clinical trials and post-marketing studies globally (January-December 2017)

#### **Our Drug Safety Functions**

In Japan and overseas, Chugai handles numerous biopharmaceuticals, molecular targeted therapies and other pharmaceuticals with innovative modes of action. To promote the appropriate use of these pharmaceuticals around the world and gain acceptance from patients and healthcare providers, Chugai establishes pharmacovigilance protocols with Roche and its other partners and collects safety information on a global level. Expert safety evaluation is also essential and we consider speedy decision-making crucial for timely provision of safety information and implementation of measures to ensure safety. Consequently, Chugai has established an independent Drug Safety Division and a system directly linked to management. Through measures such as these, Chugai is building greater credibility, with the aim of providing truly valuable safety data and contributing to patients and healthcare worldwide.

#### Measures to Enhance Drug Safety

#### Promoting Safety Evaluation and Appropriate Use

Post-marketing surveillance, which includes allcase registration surveillance, is conducted under actual treatment conditions to collect safety information unobtainable in clinical trials. In post-marketing surveillance, data on safety are collected from medical institutions through electronic systems. Information on the results obtained from analysis of this data is provided

**Organization Oriented to Risk Management** 

**RMP planning & updating** 

**Global/Local consistency** 

Risk

om the perspectiv

Signal detect Medical evaluation

Ithcare

of pati

nts and

### to medical institutions and announced via scientific conferences, papers and other means.

12 products

RMPs prepared and carried out for

thorough risk management

(As of February 2018)

Numerous anticancer agents, innovative new biopharmaceuticals and other drugs require wider-ranging and more rigorous management, such as thorough management of distribution and confirmation of conditions of use, in addition to all-case registration, in which all patients administered a product are registered. In addition to rigorous safety measures, Chugai has been conducting all-case registration surveillance ahead of other companies, for Avastin, Actemra, Alecensa and other products. With this extensive experience, we lead the industry in drug safety evaluation and safety measures.

#### Leading the Industry through **Risk Management Plans**

As pharmacovigilance activities and discussions have picked up worldwide in recent years, Chugai has established a world-class safety management system that can accommodate the pharmaceutical regulatory systems and review procedures of regulatory agencies in Japan, the United States and Europe. Moreover, to establish a plan – do – check – act (PDCA) cycle for our post-marketing pharmacovigilance activities and measures to ensure safety, we collect and analyze information consistently from the preclinical and clinical stages, and have drawn up and applied risk management plans (RMPs) to several of our products since 2012, ahead of our competitors. We consider RMPs to be part of our commitment to patients and healthcare providers

Safety measures,

Patients

Media

ection and accumulat of safety information

sion of informat

Medical institutions

Regulatory agencies

#### Safety Evaluation and Communication

20

Papers and conference

presentations on safety

(2017)

Chugai is committed to highly transparent and speedy reporting and release of drug safety information. We collect a large volume of safety information from countries around the world and evaluate it from a medical standpoint. We have established a system for recording the information in a database and conducting signal detection of adverse drug reactions using that database. With this system, we promptly consult with regulatory authorities in each country regarding safety measures. In addition to this large volume of safety information, we have in-house medical doctors with abundant clinical experience who also conduct expert safety evaluations.

To provide diversified and sophisticated solutions, we restructured our organization in April 2017 to enhance communication with customers and increase our capacity to generate safety information using advanced technologies such as epidemiology and information technology. In applying RMPs, we believe we need to strengthen our ability to analyze data from an epidemiological standpoint. To achieve this, a specialized internal group in charge of epidemiology functions is cooperating with specialized companies and others to help upgrade Japan's epidemiological database. We are also driving the industry in ways such as proactively working to formulate industry-wide recommendations and guidance for database research.

For communications with customers, we provide information on noteworthy adverse drug reactions to medical institutions and academic societies. We also distribute information leaflets for patients to medical institutions, post information on our website, hold presentations for pharmacists and conduct media seminars. In April 2017, we also established the new specialist position of Safety Expert for handling safety information to engage in more detailed communication tailored to the needs of each customer and the healthcare characteristics of each region. We will continue to enhance delivery of information using ICT-based tools to help healthcare providers better navigate patient treatments, thus helping to steadily reduce the incidence and severity of adverse drug reactions.

### Intellectual Property

#### Initiatives and Performance in 2017

4,219 Number of patents held (including pending applications) (As of December 31, 2017)

188 New patents granted worldwide (2017)

#### Implementation of Our **IP Strategy**

Chugai views its global intellectual property (IP) strategy as the foundation for creating innovative new drugs. By integrating it with our business and R&D strategies, we protect the competitive advantage of our products and ensure operational flexibility. We focus resources on and secure IP rights for high-priority R&D projects. At the same time, we actively work to secure rights outside Japan with a view to global co-development with the Roche Group. When we apply for patents for products, we include filings for our inventions related to formulation, production method, diagnostic method and personalized healthcare in addition to those for the substance and use. We also work to establish rights globally for significant drug discovery technologies such as innovative antibody technologies, and use those rights in planning and executing our IP strategy. In addition, we are building our own database for patents related to antibody engineering technologies, which are becoming increasingly complex and sophisticated, and are using this database to plan IP strategies, including monitoring trends at other companies.

#### **Our IP Strategy**

One feature of our IP strategy is that we take full advantage of our benefits as a member of the Roche Group. For inventions originating at Chugai, we take responsibility for planning and execution of matters such as application strategies for individual products, selection of countries where applications will be filed, and strategies for acquisition of rights in Japan and overseas. In addition, we endeavor to choose our best options globally by coordinating closely within the Roche Group, including with Genentech, at all times.

Another feature is our strategic use of antibody-related technology patents. Antibody engineering technologies are an important part of our R&D strategy, and we actively conduct research and development both to cultivate our basic technologies and to apply them to product development. Under our IP

the strategic use of our antibody-related technology patents by building a database of antibody sequences developed by third parties, and by monitoring the status of antibodies (relevant to our patents) being developed at competitors. In this way, we aim to secure a competitive advantage in the market.

### **Current Patent Portfolio**

By therapeutic area, oncology accounts for the largest share of our patent portfolio with approximately 29 percent of the total, a proportion that reflects our product

#### Number of Patents Held (Including Pending Applications) and New Patents Granted



#### **Dispatch of IP Liaison Staff**

Ensuring operational flexibility for innovative drugs created from our own research and development projects requires integration of our IP and research strategies to introduce research resources into the white spaces (gaps) in other companies' rights and to establish our own rights in those spaces. At the same time, the intensifying competitive environment is increasing the importance of repositioning, which involves reconsidering strategies depending on changes in circumstances both internally, such as the progress of research, and externally, such as the publication of applications by other companies. With these conditions in mind, we completed a personnel deployment plan to dispatch IP liaisons to the Fuji Gotemba and Kamakura Research Laboratories in order to defend our rights in our targeted disease areas. We will continue to create more innovative products through collaboration between our research and IP functions, using our IP liaisons as a hub.

Data analysis

Study of safety measu

Epidemiology

informatio

Product profile Regulations

Healthcare trends



#### Defended the market for Oxarol Ointment with a patentinfringement lawsuit against manufacturers of generics\*

strategy, we have created a framework for

portfolio. In 2017, Chugai acquired 188 patents in Japan, the United States and major European countries, as well as other countries worldwide. These include patents protecting SKY59 and other Chugai development compounds and products, as well as SMART- Ig®, our innovative antibody technology.

\* On March 24, the Supreme Court of Japan rendered a judgment dismissing the appeal by generic drug manufacturers against Chugai's lawsuit in which it sought injunction against those companies based on infringement of the process patent on Oxarol Ointment, thereby making Chugai's victory in the lawsuit final.

# Environmental, Health and Safety Data

#### Climate Change Countermeasures (2010 is the base year for perer mid-term environmental goals.)

#### Total and Per-Employee Energy Consumption

Total energy consumption was 2,185,000 gigajoules, an increase of 15,000 gigajoules from 2016. Energy consumption per employee decreased 3 gigajoules.



#### **Resource Saving and Waste Reduction**

#### Industrial Waste

The amount of industrial waste generated was 2,854 tons, an increase of 12 percent from 2016. This is mainly attributable to a combined increase of 221 tons in waste oils, waste acids and waste alkalis due to higher production volume.



#### **Chemical Substance Management**

#### Handled Amounts of Chemical Substances Covered by PRTR Law

The handled amounts of chemical substances covered by the PRTR Law totaled 28.2 tons, an increase of 1.7 tons from the year ended March 31, 2016. The main factor was a 6.9-ton increase in acetonitrile handled, despite a decrease of 7.0 tons in N,N-Dimethyformamide from the year ended March 31, 2016.



(2010 is the base year for per-employee energy consumption and  $\mbox{CO}_2$  emission mid-term environmental goals.)

#### CO<sub>2</sub> Emissions and CO<sub>2</sub> Emissions per Employee

Total  $CO_2$  emissions were 100,604 tons, an increase of 728 tons from 2016.  $CO_2$  emissions per employee decreased 0.2 tons.



Units of energy for electricity are calculated using the coefficients in the Enforcement Regulations for the Act on the Rational Use of Energy, and the electricity emission factor is calculated using the 2005 Electricity Emission Factor for Receiving Electricity announced by the Federation of Electric Power Companies of Japan. Since 2016, the unit of energy and emission factor for each type of energy use the coefficients listed in the Enforcement Regulations of the Act on Promotion of Global Warming Countermeasures (amended March 3, 2010). For city gas consumption, the standard state conversion value is used.

#### **CFCs and HCFCs Used to Fill Equipment**

The amount of CFCs and HCFCs used was 4,646 kg, a decrease of 846 kg (15.4 percent) from 2016. Chugai is making efforts to phase out use of CFCs and HCFCs.



#### Waste Recycled and Recycling Ratio<sup>3</sup>

The recycling ratio was 76.4 percent, a decrease of 1.8 percentage points from 2016. This is mainly attributable to an increase in non-recyclable waste materials that accompanied the increase in waste generated.



3. Amount of waste recycled / Amount of waste generated

#### Water and Air Pollution Countermeasures

#### Water Consumed and Wastewater

Water consumed increased 142 thousand tons from 2016 due to the increase in production.



#### Industrial Landfill Waste and Final Disposal Ratio<sup>4</sup>

The final disposal ratio was 0.8 percent, a decrease of 0.2 percentage points from 2016. We have maintained this ratio below 2 percent since 2014.



Amount of industrial landfill waste (left scale)
 Final disposal ratio (right scale
 Amount of industrial landfill waste / Amount of waste generated

#### NOx, SOx and Ash and Dust Emissions

NOx emissions increased 9 tons from 2016, but were below the prescribed environmental limits at all sites. SOx, ash and dust emissions are trending downward as a result of the conversion of the main fuel in heat source equipment to city gas from Bunker A fuel oil.



#### **Ratio of Eco-Friendly Cars**

As of December 31, 2017, Chugai had introduced a cumulative total of 1,413 hybrid and fuel-efficient vehicles in its MR fleet. The ratio of ecofriendly cars was 78 percent, remaining above the target of 50 percent.



#### **PPC Paper Purchased**

The amount of plain paper copier (PPC) paper purchased decreased 22.9 percent compared with 2016. Factors in the decrease include reduction in the amount of printed handouts for meetings and control of printing on multifunction printers. We also continued to purchase PPC paper that is compliant with Japan's Green Purchasing Law.



#### Health and Safety Management

#### **Occupational Accident Incidence and Severity Rates**

The incidence rate is the number of occupational accidents, defined as workplace incidents resulting in illness, injury or death, per million hours worked, and indicates the frequency of such incidents. The severity rate is the number of workdays lost per 1,000 hours worked, and indicates the severity of occupational accidents.



### Social Contribution

#### Initiatives and Performance in 2017

Promoted awareness

of para-sports

1 vehicle each to 5 organizations Donation of welfare vehicles to provide transportation for home

welfare services

(2017)

Awareness

Participation in Lung Cancer

Lung Cancer Awareness is a committee

Society in November 2014 to share accurate

established by the Japan Lung Cancer

information among patients and their

families, promote lung cancer prevention

and improve the results of diagnosis and

considers it important that patients and

healthcare providers fully understand the

information necessary for their proper use.

committee's activities, we are working to

provide information that patients and

**Promotion of Measures** 

healthcare providers need.

By endorsing and actively participating in the

against Locomotive Syndrome

Locomotive syndrome is a condition in

which muscles, bones, joints, cartilage,

intervertebral discs and other parts of the

musculoskeletal system become impaired

of the syndrome is highly likely to impede

daily life. The Japanese Orthopaedic

Association proposed it as a concept in

2007 and has been working to prevent

the syndrome, establish measures for

of the Japanese Clinical Orthopaedic

life expectancy through this activity.

Support for Para-Sports

Chugai co-sponsors the Japanese Para-

Sports Association (JPSA) as an official

partner, and cooperates in activities to help

realize the JPSA's philosophy of "creating a

Chugai conducted in 2017 are as follows.

Dispatch of volunteers to competitive

Chugai held the Chugai Pharmaceutical 2017

Wheelchair Softball Tournament in Tokyo as

sports events

vital and inclusive society" The main activities

coping with it, and improve awareness. In

cooperation with the prefectural chapters

Association, Chugai holds the Bone and

Joint Forum about 10 times a year to deliver

the latest information to healthcare providers.

We will continue helping to promote healthy

and motor function declines. The progression

treatment. Chugai markets three lung cancer

agents – Avastin, Tarceva and Alecensa – and



Number of locations in which Chugai employees participated in the 24-hour charity event Relay For Life Japan (2017)

Joined global initiative Access Accelerated (2017)

the title sponsor and provided support by sending 26 employee volunteers to assist with set-up, event management, English interpreting and other matters.

#### Activities to raise awareness of para-sports

- Co-sponsorship of a chair ski school for parents and children held by the Japan Chair Ski Association
- Support for a wheelchair tennis camp for children
- Operated a booth for experiencing wheelchair tennis and chair skiing at local community events and other venues - Presentation of the para-sports-related webpages "Another Sport" and "ATHLETE MOTHERS" on the Chugai website (Japanese only)

#### Initiatives for employees and their families

To deepen understanding of para-sports and people with disabilities, Chugai held a handson event for experiencing blind sports in cooperation with the Yokohama City Special Support School for the Visually Impaired. There were 21 participants from Chugai, including employees and their family members.



Blind sports experience event

#### **Disaster Relief**

#### Support for Children in Stricken Areas

Chugai once again participated in the global charity event Roche Children's Walk conducted by Roche to support children in need. In this annual initiative, Chugai matches the total amount of funds raised by its employees, and the combined amount is donated to selected organizations. In 2017, the recipient organization was the Kumamoto City Join Hands Association, a social welfare organization conducting activities for the

developmental support of children living in areas affected by the 2016 Kumamoto Earthquakes.

#### **Charity Sale**

As part of its support for recovery from the 2011 Great East Japan Earthquake, Chugai held a charity sale at its Kamakura Research Laboratories. Presented in cooperation with the Kesennuma Fisheries Cooperative Association and FUYODO 2100, an NPO in Koriyama City, Fukushima Prefecture. the event featured specialty products from the affected area.



#### Welfare Vehicle Donation Program

Chugai's program to donate specially equipped welfare vehicles began in 1985 as part of activities to commemorate the Company's 60th anniversary. The program marked its 33rd year in 2017. A total of 248 vehicles have been donated since the start of the program.

Securing the means for senior citizens and disabled people living at home to go to places such as hospitals, day service centers and day care centers and for staff from these facilities to visit homes to perform in-house care, is significant from the viewpoint of enhancing welfare services.

The welfare vehicle donation program is conducted in cooperation with the Japan National Council of Social Welfare and Central Community Chest of Japan, and through it vehicles have been donated to recipients in all of Japan's 47 prefectures.

#### Initiatives for Global Health

As international contributions in the area of global health, Chugai participates in the Global Health Innovative Technology Fund (GHIT Fund),<sup>1</sup> which aims to conquer infectious diseases in developing countries, and Access Accelerated,<sup>2</sup> which conducts measures for people in those same countries who are living with noncommunicable diseases (NCDs). 1. For details, see the GHIT Fund website (http://www. ahtfund.ora/en).

2. For details, see the Access Accelerated website (http://www.accessaccelerated.org/)

#### **GHIT Fund**

Jointly established in April 2013 with donations from Japanese pharmaceutical companies, the Japanese government (the Ministry of Foreign Affairs and the Ministry of Health, Labour and Welfare), the Bill & Melinda Gates Foundation and the United Nations Development Programme, the GHIT Fund is Japan's first public-private

#### For the Future of Generation AYA Members Living with Cancer Launch of "AYA Life" for Adolescent and Young Adult Cancer Patients and their Families

In March 2017, Chugai launched "AYA Life," a website for young cancer patients, with the aim of "realizing cancer treatment that allows patients to confront cancer proactively and with hope." AYA, an abbreviation of "Adolescent and Young Adult," refers to the population from around 15 to 39 years of age. There are fewer cancer patients in this age group than in older generations, making it difficult for them to find someone with the same disease to talk to, places for counseling, or information specific to their own generation. To help resolve such problems, the website includes a section where patients from Generation AYA talk about their experiences, a page providing help in building a support network and a "Generation AYA Q&A" section. Future progress in support measures is expected given the inclusion in the Japanese government's Third-Term Comprehensive Ten-Year Strategy for Cancer Control of an examination of improvements to systems to provide がんと生きているAYA世代の未来のために information and support counseling and employment for Generation AYA cancer AYA Life patients. As a leader in oncology in Japan, Chugai will continue to carry out activities that are trusted and valued by healthcare providers, patients, and their families

(For details, see https://aya-life.jp/ (Japanese only))

**Basic Approach** 

As a responsible pharmaceutical company in healthcare, we proactively engage in activities such as raising awareness of diseases and disseminating pharmaceuticals in developing countries.

In the area of welfare, in conjunction with our business activities in the renal and bone and joint areas, we conduct ongoing donations of specially equipped paratransit vehicles as we understand the importance of transportation assistance services for people who require in-home nursing care. We also support parasports to create a society where everyone can be active through sports. Regarding education, as a company that deals with leading-edge science we conduct activities to raise awareness of science and medicine among students, from elementary school children to university students, as well as among adults. Moreover, we cooperate with local communities and engage in disaster preparedness education, mainly in areas where our research laboratories and plants are located.

#### **Disease Awareness**

Chugai participates in and co-sponsors a variety of activities to support cancer patients and their families. One such activity is Relay For Life Japan, an awareness support campaign that forges ties in the fight against cancer. This event, a 24-hour walk-a-thon in which cancer patients, their families and supporters compete as relay teams, was held in 49 locations throughout Japan in 2017. Chugai employees have participated as volunteers in Relay For Life Japan since 2007. A total of 490 employees took part as "Team Chugai" at 29 locations in 2017. For its disease awareness activities, Chugai used augmented reality (AR) to present "Go into the Stomach! - Search for the Seven Secrets," in which a total of 1,499 people took part at 23 locations. While Team Chugai members provided explanations, participants learned about matters related to stomach cancer that appeared on the screen and deepened their understanding of the importance of early detection and treatment.



partnership to support and promote research and development of drugs, vaccines and diagnostics for infectious diseases in developing countries.

In December 2014, Chugai announced its participation in the GHIT Fund and contributed capital. It also decided to undertake a specific drug development program using its innovative discovery technologies and research resources. As a partner in the GHIT Fund, Chugai expects that furthering the development of new medical technologies will go beyond fulfilling its basic social responsibility, leading to the promotion of health and sound economic growth in developing countries.

#### Access Accelerated

Access Accelerated was established in January 2017 by 22 global pharmaceutical companies including Chugai at the World Economic Forum Annual Meeting held in Davos, Switzerland. In partnership with the World Bank Group and the Union for International Cancer Control (UICC), Access Accelerated is working to achieve the UN Sustainable Development Goal 3 target of reducing premature deaths due to NCDs by one-third by 2030.

Approximately 80 percent of NCD deaths occur in low and lower middle-income countries. Ensuring access to medicines in those regions is a key issue for sustainable improvement in the health of the working population. Through participation in Access Accelerated, Chugai will extend its efforts to healthcare and health in developing countries.



### Corporate Communication

Initiatives and Performance in 2017

16 Information events for the media and institutional investors (2017)



Security analysts and institutional investors worldwide with whom individual meetings were held (2017) Briefings for individual investors and shareholders (2017)

8



(2017)

Communication with Society

Chugai emphasizes communication with stakeholders to increase its corporate value. We are therefore working to enhance communication not only with our shareholders and investors, but also with the general public.

As part of these efforts, Chugai shares its unique strengths outside the Company to gain recognition and understanding. (See "Chugai's Seven Strengths" on pages 10-11 of *Our Essence* for details.)

INNOVATION BEYOND IMAGINATION: This corporate slogan conveys the commitment of the Company and the strong desire of its employees to make Chugai a top pharmaceutical company that continuously creates not only the products anxiously awaited by people around the world but also unprecedented medicines that exceed all expectations.

#### Media Relations

Chugai conducts proactive media relations through methods including press releases, various types of information meetings and informal discussions with management. We particularly concentrate on meeting individually with reporters covering the Company or the industry for the first time and providing them with basic information to further heighten their interest in and understanding of Chugai and the pharmaceutical industry. Recognizing the important role played by the media in conveying information to stakeholders, Chugai works to maintain good relationships with media outlets while disclosing information appropriately and in a timely manner. In 2017, Chairman Nagavama initiated information meetings for the media with a presentation of his approach to the challenges faced by the Japanese pharmaceutical industry in generating continuous innovation

### Communication with Shareholders and Investors

The 106th Annual General Meeting of Shareholders was held on March 23, 2017. After the presentation of the business report through video and other materials, shareholders deliberated on agenda items concerning appropriation of retained earnings, election of directors and Audit & Supervisory Board members, and the amount and details of remuneration to be paid to directors in the form of shares with restriction on transfer. All agenda items were approved and passed by a majority. The General Meeting of Shareholders is available on demand as a streaming video (in Japanese only) on our website for shareholders who did not attend. In addition, convocation notices for the General Meeting of Shareholders are normally sent out more than four weeks prior to the meeting date.

Coinciding with financial results announcements, Chugai holds information meetings and conference calls for investors, analysts and the media. During 2017, we held "R&D conference calls" to explain and answer questions about information of great interest to investors related to international conferences on oncology and hematologic diseases, held in June and July, respectively. To increase communication with individual shareholders, Chugai has conducted tours of its Utsunomiya Plant each year since 2013, and is enhancing its outreach to them by holding information meetings at branches of securities companies in Japan.

Senior management also continued to hold overseas roadshows and, in addition to their visits to institutional investors in the United States, Europe and Asia, Chugai IR Group employees conducted roadshows as an additional initiative to cultivate new institutional investors, mainly in North America and Europe. To deepen mutual understanding between Chugai's President and market participants through direct communication in small groups, President Kosaka held informal discussions with investors and analysts in 2017.

Due to the introduction of the Principles for Responsible Institutional Investors (Japan's Stewardship Code) and Japan's Corporate Governance Code, greater dialogue between companies and shareholders is required. The Japan Securities Dealers Association has established guidelines for securities companies' analysts in activities related to obtaining information from issuers and providing it to investors, and voluntary restrictions have been introduced on obtaining information from issuing companies prior to earnings announcements, among other measures. As a result, although the number of individual interviews decreased, Chugai has proactively established forums for discussion between

investors and its management team for a fuller exchange of opinions on the Company's vision and medium-to-long-term strategies. We will continue measures to enhance face-to-face IR with management to promote understanding of Chugai's corporate value.

#### **Disclosure Policy**

Chugai conducts interactive corporate communication activities to deepen mutual understanding and build relationships of trust with its stakeholders, such as patients, healthcare providers, shareholders, investors and employees. In order to achieve these objectives, Chugai ensures that information related to its business activities is made available to stakeholders in a transparent, fair and consistent manner.

Chugai's policy for disclosing information to shareholders and investors is to make timely, appropriate and fair disclosure of information in accordance with the Financial Instruments and Exchange Act and relevant rules of the stock exchange on which Chugai's shares are listed in order to receive fair valuation in capital markets. In addition, measures to allow easy access to disclosed information have been established to ensure transparency. As a rule, we disclose information simultaneously in Japanese and English, and endeavor to provide information in a prompt and fair manner in Japan and overseas.

Chugai has established an IR Committee composed of the CFO and general managers of the Corporate Communications Department, the Corporate Planning Department, the Finance & Accounting Department, the Corporate Social Responsibility Department and the General Affairs Department as a corporate management committee. The IR Committee holds regular meetings and is responsible for the establishment, revision and internal dissemination of the Disclosure Policy, and for the management and promotion of information collection, disclosure and other related activities. Top management, including the CEO and key executive officers, has primary accountability for disclosure. In addition, the Corporate Communications Department takes the lead in coordinating with relevant departments to disclose information promptly.

Note: For further details on the Company's policy for disclosure to shareholders, investors, securities analysts and other capital market participants, please refer to the Chugai website (https://www.chugaipharm.co.jp/english/ir/policy/disclosure.html).